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A SYMPOSIUM ON THE CRITICAL STATE[1]

THE CRITICAL STATE OF PURE FLUIDS

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If a closed tube which is only partly full of ether, alcohol, or other pure liquid is heated uniformly and not too rapidly, certain interesting phenomena may be observed. If ethyl ether is used and the tube is about one-third full when cool, the volume of the liquid does not change very much during the heating. As the temperature is raised the curved meniscus or boundary between the liquid and vapor flattens slightly and then more rapidly, becomes quite flat and indistinct, and finally fades out entirely without ebullition.

Figure 1 shows a series of instantaneous photographs[2] of such a tube at different temperatures. The numbers under the photographs indicate the temperatures at which the different photographs were taken, with the temperature of disappearance of the meniscus taken as the temperature of reference. This temperature is called the critical temperature, which for pure ethyl ether is almost exactly 194°C. For ordinary impure ether, the temperature may be a few degrees higher.

If, as in figure 2a, the tube is more than one-half full when cool, the meniscus rises and eventually the tube is completely full before the critical temperature is reached. If, on the other hand (figure 2b), the tube is much less than one-third full, the meniscus sinks and the liquid disappears entirely before the critical temperature is reached.

If, after the meniscus has disappeared, the tube of figure 1 is cooled and the temperature 194°C. is approached, the material in the tube becomes opalescent (see figure 3). The opalescence increases until suddenly a cloud forms and the meniscus reappears out of the cloud. The amounts of opalescence and cloud depend on the manner of heating. If the liquid is brought very slowly just past the critical temperature and then cooled, the opalescence is slight and the cloud appears in the opalescent region. If the material in the tube is carried, say 20°C., above the critical temperature or held a little above the critical temperature and stirred, the opalescence and cloud fill the tube. For the latter case observation has shown that the cloud forms first at the bottom of the tube and grows upward. Usually the opalescence changes to a deeper color, and becomes almost brownish; then the material suddenly turns white as the cloud forms.

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[1] This Symposium was presented before Section III (Chemical, Mathematical, and Physical Sciences) of the Royal Society of Canada at Ottawa, Canada, May 21, 1936, under the chairmanship of the President of the Section, Dean A. L. Clark, F.R.S.C.

[2] The light required for photographing the tube creates some heat, which introduces complications. The phenomena portrayed, however, represent fairly truthfully what takes place under more ideal conditions.

The cloud persists after the meniscus forms; on careful examination it

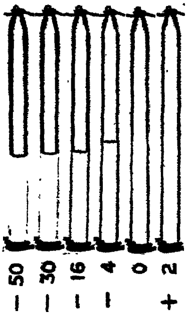

FIG. 1

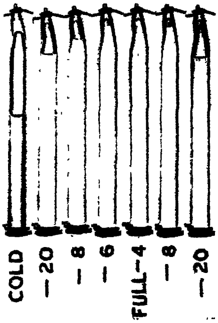

FIG. 2a

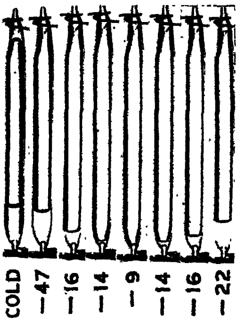

FIG. 2b

FIG. 1. Phenomena observed when a closed tube partly filled with ethyl ether is heated.

FIG. 2a. Closed tube containing ethyl ether. The tube is more than half full when cold; at 190°C. the liquid fills the tube.

FIG. 2b. Closed tube containing ethyl ether. The tube is much less than one-third full when cold; at 185°C. the vapor fills the tube.

is seen that above the meniscus there are innumerable droplets of liquid falling through the vapor and that below the meniscus bubbles of vapor are rising through the liquid. The temperature of reappearance of the meniscus seems to be a fraction of a degree below that of disappearance, although it may be that this is not always true.

Figure 4 shows the difference in the appearance of the cloud for the two cases mentioned above. The tube of the first pair of photographs was heated just past the critical temperature and cooled immediately. The first photograph of each pair was taken just as the cloud formed and the second when it was at the maximum, a few seconds later. The tube of the second pair was heated 24°C. above the critical temperature and cooled.

An interesting variation of the experiment may be made by inserting a capillary tube in the larger tube (figure 5). As the temperature rises the capillary height in the small tube diminishes, until at the critical temperature the level is that in the outer tube, when both surfaces are flat. If the heating is rapid the small meniscus may lie below the larger. This is due to unequal densities within and without the capillary.[3]

Even after the meniscus has become invisible when the tube is viewed directly, it may be seen from above or below, sometimes shining like a perfect mirror, sometimes appearing as a dark patch (figure 6), the appearance depending on the temperature and the angle of vision. Two photographs are shown, one taken looking down at an angle, the other horizontally. In one the meniscus is plainly seen, in the other it is invisible.

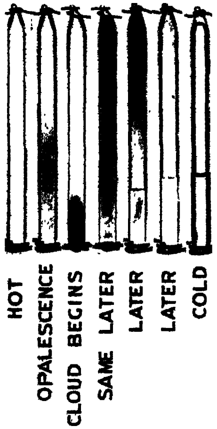

FIG. 3

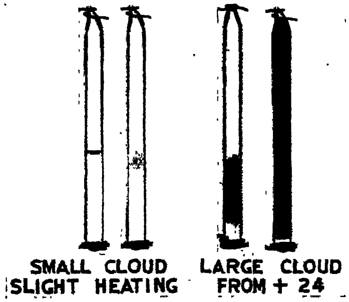

FIG. 4

FIG. 3. Phenomena observed when the tube of figure 1 is cooled
FIG. 4. Formation of cloud

The disappearance and reappearance of the meniscus at a particular temperature are known as the Cagniard de la Tour (15) phenomena. These phenomena were observed for a number of liquids by different experimenters, but until the work of Andrews (1869) their significance was not recognized. Andrews' work on carbon dioxide led to an almost complete understanding of the conditions under which a gas may be liquefied. Faraday had much earlier given the name "permanent gases" to those gases which he was unable to liquefy by the methods of his day.

The Andrews (1) experiment consisted in compressing carbon dioxide at constant temperature and measuring the pressure and volume over a wide range of volumes. At low pressure and not too high temperature the pressure–volume curve is not unlike that for a perfect gas. This is the unsaturated vapor pressure curve. If the volume is much decreased Andrews found that at a certain volume, varying with the temperature, the gas begins to liquefy and continues to do so as the volume is still further reduced, until the vapor is all condensed. During this part of the experiment the pressure remains strictly constant, so that the vapor pressure line is straight and horizontal. This corresponds to the two-phase equilibrium state of the substance. Further reduction of volume is attended by an extremely rapid rise in the pressure, since liquids are highly incompressible. The entire curve outlined above is an isothermal line and consists of the three parts described.

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[3] Those who have been fortunate enough to see liquid helium no doubt have been struck with the extreme flatness of the surface. The liquid and vapor are so near the critical temperature that the surface tension at their interface is very small.

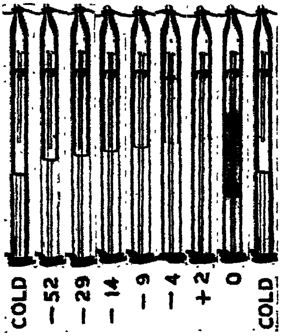

FIG. 5

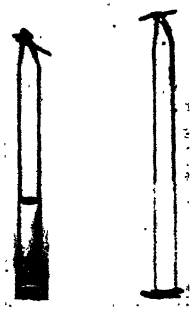

FIG. 6

FIG. 5. Disappearance of surface tension

FIG. 6. Photographs of the tube at the time when the meniscus is invisible when viewed directly. One photograph was taken from above, looking down at an angle; the other horizontally.

If the experiment is repeated at a higher temperature the straight part of the isothermal becomes shorter, until at a certain temperature it shrinks to a point. Andrews called this temperature the critical temperature; it corresponds to the temperature so named in the early part of this paper. The isothermal for this temperature is called the critical isothermal. The point at which the ends of the straight line have drawn together is called the critical point. The terms "critical pressure" and "critical volume" are self-explanatory. We have also critical volume, critical index, and a variety of other names for properties exhibited by the substance at the critical point. The critical temperature was called the absolute boiling point by Mendelejeff.

Van der Waals (16) in 1881 made an important contribution to the knowledge of liquids and vapors, particularly near the critical point. He was able to give, on grounds at least partly theoretical, the first moderately satisfactory equation which gave a comprehensive description of the behavior of liquids and vapors under varying pressures and temperatures. This well-known equation is really the equation of the isothermal line with the temperature taken as a parameter.

According to the work of Andrews and of van der Waals the properties of the liquid and vapor become identical at the critical point, a most important fact about this point. Also, according to their theory, the liquid state does not persist above the critical point. At the critical point liquid becomes vapor without evaporation and no liquid is possible above this point. The densities of the two phases merge into each other at the critical point (figure 7). This is a very significant fact and certainly points to homogeneity at this point. It will be noticed that the most important part of the curve is dotted, which indicates that the last stages of the curve were drawn in without data. It is precisely in this region that accurate observation is required.

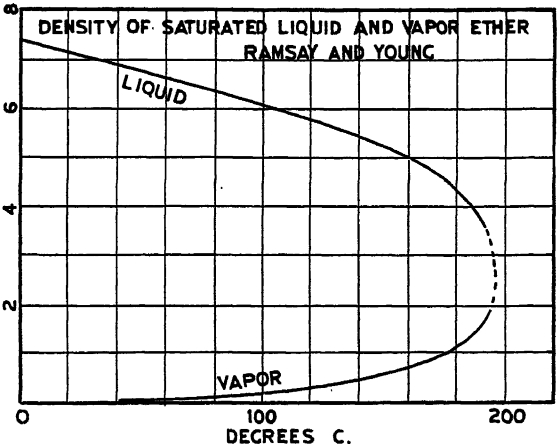

Fig. 7. Plot of the density of the saturated liquid and vapor of ether (Ramsay and Young).

The work of Andrews and of van der Waals seemed not only to establish the identity of phases at the critical point but to yield the additional fact that there could be no liquid above the critical temperature. These two facts may be said to represent what has come to be known as the classical theory of the critical state.

Experiments seemed to show that the surface tension of liquid and vapor become identical at the critical point (figure 5) and that the densities become equal also (figure 7). There can be no doubt about the existence of a surface tension at the boundary surface of a vapor. If the surface tensions of liquid and vapor become equal, the interface could hardly exist, and if the densities become equal the phases might intermingle. Equality either of surface tension or of density need not mean that liquid has disappeared entirely, but it was generally believed that such was the fact.

Presently difficulties appeared. Many observers, e.g., Cailletet and Colardeau (2), Hannay and Hogarth (8), and Hagenbach (7) (to mention only a few of the earlier ones) began to produce what seemed to be evidence that the liquid state may persist above the critical temperature, i.e., that the critical temperature does not mark the end of the liquid state. The belief grew that the vapor phase was really only largely vapor with liquid mixed with it and that the liquid phase contained some vapor mixed with it. At the critical point the two mixtures became identical. Liquid, according to these observers, persisted far above the critical temperature and gradually disappeared. Further, they claimed that at a constant temperature above the critical, the liquid part of the mixture gradually disappeared, in part if not completely.

Many different methods were employed to show the persistence of liquid above the critical point. Hannay and Hogarth added coloring matter to the liquid and found that above the critical temperature the substance in the lower part of the tube was more strongly colored than that in the upper portion of the tube. Others added a salt to the liquid to make it electrically conducting and found that above the critical temperature the lower part of the tube remained more strongly conducting than the upper part.

Another experiment, which was thought to give support to the objections to the classical theory, involved the estimation of the densities of the phases above the critical point by observing the amounts of liquid after condensation. For example, if a tube in the form of an inverted U (figure 8), in which the liquid is originally all in one arm, is heated through the critical temperature and cooled, then above the critical temperature, according to the classical theory, the vapor should be homogeneous throughout the tube and after cooling there should be equal amounts in the two arms. As a matter of fact the distribution in the arms is far from equal. Much more is found in the arm in which the liquid was present before heating than in the other, even when the heating is carried far above the critical temperature or when the heating is continued for a considerable time above the critical temperature. This seems to indicate that the liquid state has persisted above the temperature at which it should disappear.

Then there is the experiment of Cailletet and Colardeau with a continuous tube in the form of an elongated O (figure 9), in which mercury or some other liquid is placed to act as a differential manometer. If more of the liquid under experiment is placed in one side than in the other the difference in the levels of the manometric liquid measures the excess. If the tube with its contents is heated above the critical temperature this difference in level is maintained, at least in part, well above the critical temperature and for a considerable time.

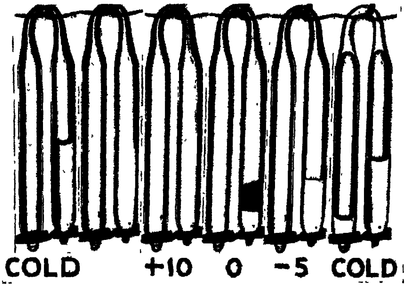

FIG. 8

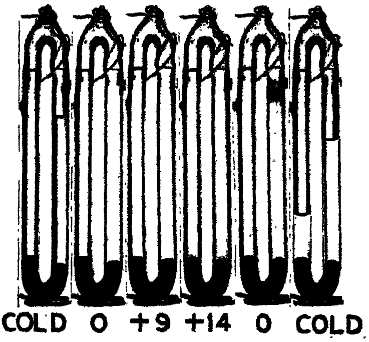

FIG. 9

FIG. 8. Phenomena observed when the liquid, in an inverted U-tube, is heated through the critical temperature and then cooled.

FIG. 9. Phenomena observed when the liquid, in an elongated O-tube containing mercury to act as a differential manometer, is heated above the critical temperature.

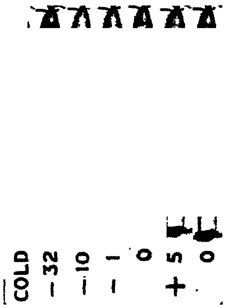

FIG. 10. Effect of temperature on the index of refraction of liquid and vapor

The indices of refraction of the liquid and vapor are in general different from each other. If a straight vertical tube is partially filled with the fluid (figure 10) and the image of the tube is projected on a screen the difference in the refraction by liquid and vapor is very noticeable. The line of light above the meniscus is not of the same width as below and the break is sharp. If the tube is heated the vapor becomes denser and the liquid less dense, and the indices of refraction change with the densities, so that the band of light alters in width. At the critical temperature the discontinuity in the line of light should disappear and the line become uniform. This does not happen, but the discontinuity persists although it is not as sharp. Even at temperatures well above the critical temperature the difference is easily seen.

Examples of the departure of experiment from theory need not be multiplied. Two more, however, should be mentioned. An experiment performed by de Heen (9), in an apparatus provided with movable pistons by which the amounts of liquid and vapor in the tube could be varied and with stopcocks to hold these amounts constant, seemed to show that the densities of liquid and vapor could be very different at the critical point and that the density was not a fixed quantity as had been supposed.

Finally, to complete the list, Teichner (14) actually measured the density of the fluid at different levels by the use of small, hollow glass spheres of different buoyancies, and found great differences between the densities at different levels in the tube.

All of these results seemed to lead to the general conclusion that the critical state is not the unique state that it had been believed to be and that the liquid state may persist above the critical temperature, as already noted. The phases may become alike, but the heavier portion of the phases might be expected to be present in the lower part of the container in relatively large quantity and the lighter portion in the upper part of the tube.

From these results came the theory of de Heen and Traube that each of the two phases, while different in composition, was made up of two components. They imagined two different kinds of molecules, the "liquidogenique" and "gazogenique", or liquid-forming and vapor-forming, molecules. The former were thought to be groups of the latter, and the process of passage from liquid to vapor was thought to be merely the breaking up of the larger molecules into the smaller.

According to this theory the liquid at ordinary temperatures is made up for the most part of the larger molecules, but there are always some of the smaller. The reverse is true for the vapor. As the temperature is raised, the number of small molecules in the liquid increases while the number of the larger type in the vapor increases. At the critical point the two phases become identical, but there are still many of the liquid-forming molecules present. These may break up slowly near the critical temperature, but they persist in considerable quantity at a relatively large distance above the critical temperature. When the vapor is cooled down through the critical temperature there is a reforming of the liquid-forming type of molecules into a true liquid.

This theory gained some support and seemed to explain most of the anomalies observed by so many experimenters. It was attacked, however, by Kamerlingh Onnes and his colleagues at Leiden and by others who claimed that the theory was not coherent and was really unnecessary. Kamerlingh Onnes and Fabius (13) repeated Teichner's experiment and seemed to prove that these marked differences of density do not exist if sufficient care be taken in filling the tubes with pure gas-free liquid.

So the problem was not entirely settled. In an attempt to settle this controversy the writer (4) began some years ago a study of viscosity in the neighborhood of the critical point. Viscosity is a phenomenon depending on the masses of the molecules and so might be expected to throw some light on the problem.

While ethyl ether from some points of view is not an ideal substance for investigation of the critical point, it has a low critical pressure and a fairly low critical temperature. Also it has been studied extensively.

A gold cylinder was suspended by a hard drawn silver wire (figure 11), in a tube in the form of an inverted U which contained the liquid. The cylinder had a small iron pin imbedded in a transverse position so that it might be oriented by means of an external magnetic field and would perform angular oscillations when released. The surface of the cylinder was highly polished and a spiral line was ruled on it. When a narrow beam of light was directed on to the cylinder, the ruled line appeared as a dark point on the line of light. When the cylinder oscillated this point moved up and down with a damped harmonic motion. By observing the excursions of this spot by means of a low-power telescope with an eye-piece scale, the decrement was easily calculated.

For the purpose in hand it is not necessary actually to calculate the coefficient of viscosity. The changes in viscosity may be followed through the values of the decrement just as well as through the changes in the coefficient itself.

Generally speaking, the decrement of the oscillations in the liquid decreases steadily with rising temperature until about the critical temperature, and then it increases. In the vapor the decrement increases slowly until near the critical temperature and then it increases more rapidly. It does not become as large, however, as the decrement in the liquid side of the tube. With falling temperature the decrement in the liquid side (figure 12) falls off rapidly and does not follow the values on the rising curve,—it is always lower. That in the vapor side is also less for falling temperature than that for rising temperature. If the amount of liquid in the tube is less than that which gives the critical volume, these four decrement curves apparently coincide.

Finally, if the temperature is maintained constant at a point slightly above the critical temperature, the decrement in the liquid side of the tube decreases steadily, while that in the vapor side at first increases and then

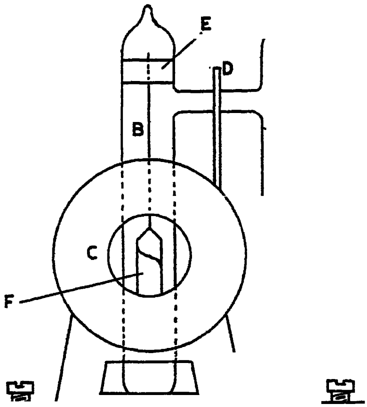

Fig. 11. Apparatus used in studying viscosity near the critical point. A, liquid; B, vapor; C, directing coil; D, support; E, suspension wire; F, gold cylinder.

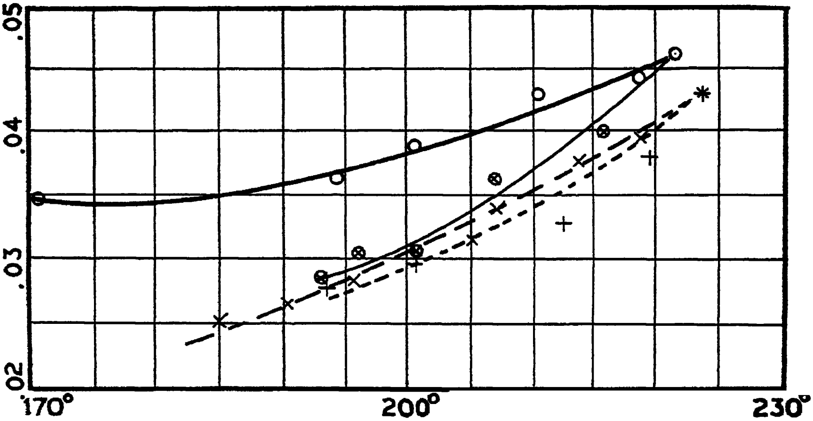

Fig. 12. Plot of the decrement of the oscillations in the liquid and the vapor against the temperature. ○, liquid up; ⊗, liquid down; ×, vapor up; +, vapor down.

decreases (figure 13). All of these results seemed to support the theories of de Heen and Traube.

As already noted, if the volume of the liquid in the tube when cold exceeds 50 per cent of the total volume, the tube is completely filled before the critical temperature is reached. Such a tube was made and results with the liquid were the same as before, only more pronounced. The decrement on the down grade is much less than on the up. The effect seems to be present for many degrees above the critical (in one case 70°C.). There is a point of discontinuity on the down curve at 194°C. (the critical temperature) (figure 14), which indicates that although there was no opalescence or cloud, *there was a marked change in the decrement, indicating a change in structure.* Objections to these results appeared shortly, based on the claims that the liquid was not sufficiently pure and that the changes in viscosity might be caused by flow of the substance from one leg of the tube to the other.

50 100 150
MINUTES

Fig. 13. Plot of the decrement of the oscillations when the temperature is maintained constant at a point slightly above the critical temperature. O, liquid at 194.0°C.; ×, vapor at 194.1°C.

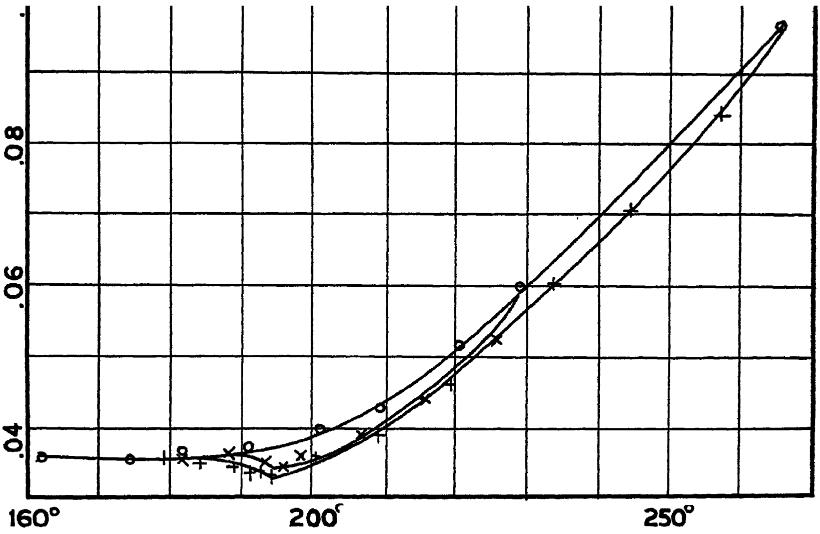

Fig. 14. Plot of the decrement of the oscillations against the temperature, using a tube containing enough liquid so that its volume when cold exceeds 50 per cent of the total volume. O, up; ×, down from 229.2°C.; +, down from 265.1°C.

Two points, however, were not made clear. Why does the viscosity of the vapor after an initial increase show a later decrease when held at constant temperature, and why is the down-grade curve for the vapor always lower than for the liquid?

In accordance with a suggestion made by Kamerlingh Onnes a tube was made in the form of an elongated O and a stirring device provided so that the material in the tube could be thoroughly mixed (5). The stirrer occupied one branch of the tube (figure 15), and the cylinder of the previous experiment the other. The top of the stirrer was made of soft steel and was hollow. The stirring was accomplished by small cups like anemometer cups, on a wire attached to the steel. All was gold-plated. A flat coil placed above actuated the stirrer, and a commutator which could be run at any desired speed controlled the rising and falling of the stirrer. Rather rapid circulation resulted from the motion. The ether used was purified with extreme care.

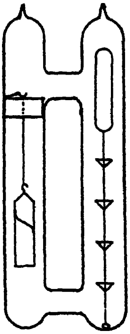

FIG. 15. Closed tube containing stirring device

Without the stirrer working, the results of the experiments were the same as before. When, however, the stirrer was operated vigorously before observations were taken, the previous results were almost absent. The values of the decrement in the liquid side and vapor side became practically the same at the critical temperature. It must be stated that the accuracy of these later results was not as great as of the earlier ones (figure 16), as the cylinders were not as well made.

The earlier work seemed to show that the liquid state does persist above the critical temperature, while the later results seemed to support the classical theory. These last results and the confirmation to some extent at least of the dicta of very weighty authorities compelled the author to accept the validity of the classical theory, but with some reluctance and misgiving.

The objections to the classical theory and the arguments against them may now be summed up.

(*a*) In the first place, according to the work of van der Waals, there is one and only one critical point where the temperature, pressure, and volume have unique values. So when the tube is partly filled with a liquid this liquid should, if the filling is less than for the critical volume, evaporate away before the critical point is reached, or should expand and fill the tube if the filling is greater than this value. There is, however, a wide range of amounts of filling between which the critical phenomena observed by Cagniard de la Tour are to be observed. For ethyl ether any amount of filling between 28 per cent and 48 per cent (6) of the total volume will show these phenomena.

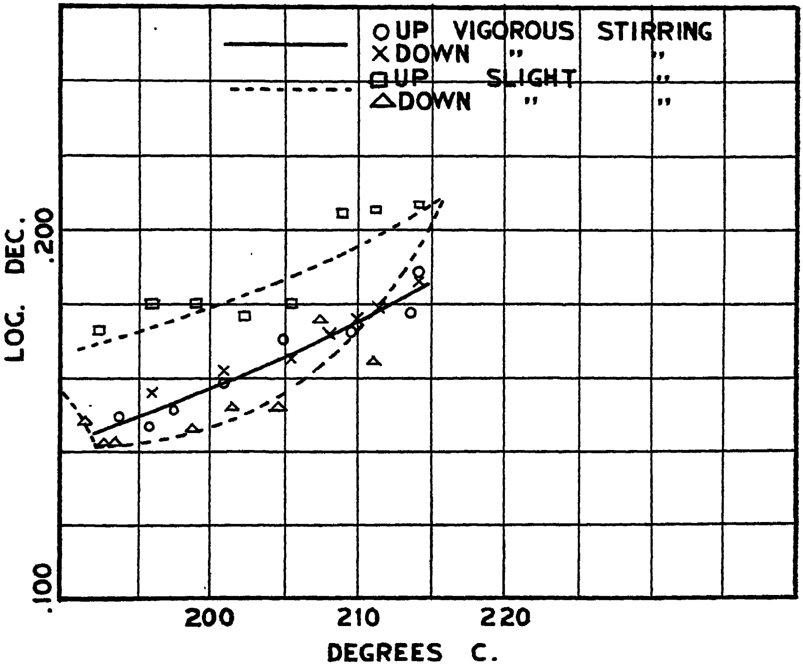

FIG. 16. Plot of the values of the decrement of the oscillations (obtained using the tube shown in figure 15) against the temperature.

(*b*) The density in the lower part of the tube is very much greater than in the upper, even above the critical temperature. This is shown by actual density determinations and by the refraction of light.

(*c*) When the temperature is lowered through the critical temperature, fog may appear in a small portion of the tube and not throughout. The amount of fog depends on the extent to which the temperature is carried above the critical temperature and on the time of heating as well.

(*d*) Coloring matter dissolved in the liquid is unequally distributed in the tube above the critical temperature. Electrical conduction as well is unequally distributed.

(*e*) The U-tube and O-tube experiments show that more fluid is found in one leg of the tube even at temperatures considerably above the critical.

(*f*) The experiments of de Heen and Traube showed different densities at different levels in the tube above the critical temperature.

(*g*) The experiments of de Heen and Dwelhauvers-Dery (10) with complicated apparatus showed non-uniform values of the critical density.

(*h*) Finally, the results of the author's work showed that the viscosity of substances in the region originally occupied by liquid remains much larger than that of the vapor and is less in both liquid and vapor after heating. Also, when kept at uniform temperature the substance in both regions shows changes in viscosity of such a character as to indicate a change in molecular structure.

(*i*) Opalescence points unmistakably to a heterogeneity of some kind.

What has been said in reply? Kuenen (11) pointed out a very important point which should be stated first. He said that nearly all of the phenomena observed may be regarded as transition phenomena which would or do disappear upon stirring and that if final states after stirring are dealt with most of the abnormalities disappear. It has been shown by many observers that when the substance is agitated or if time enough is allowed, nearly all of the abnormalities do disappear. Not all of them disappear, however. Stirring is imperative if we are to overcome the very great sluggishness of matter near the critical point.

Owing to the very great compressibility of the substance in the critical region, gravity will have considerable effect in producing an unequal distribution of density. Then again, small amounts of impurity introduced by the experimental method or by insufficient care in preparation may cause relatively large effects.

The magnitude of the effect of gravity will depend on the height of the column of fluid. From the shape of the isothermal it is possible to calculate—roughly at least—the densities at different levels. Gouy calculated that in a tube 4 cm. long containing carbon dioxide at critical filling the density may be 6 per cent greater at the bottom of the tube than at the top. Kuenen investigated this point experimentally, and found that his results agreed with this calculation. This point then may be regarded as settled.

Kuenen also investigated the effect of impurities and found that the first traces of gas mixed with pure liquid produce relatively enormous changes in the differences in density between the bottom and the top of the tube and claimed that if the liquid is not pure the differences are accounted for by the effect of gravity. From a study of the isothermals of carbon dioxide and oxygen, Verschaffelt showed that at the critical temperature with a molecular concentration of an impurity as small as 0.0001, the departure of the density from the mean may be nearly 17 per cent and that at 3°C. above the critical temperature the departure may be 5 per cent. At the critical temperature a difference of 0.001 in the concentration may cause a departure of 30 per cent from the critical density. If the density is greater or less than the critical density, as at the bottom and top of the tube, respectively, the effects are very much less.

The properties of mixtures near the critical point differ so widely from those of pure substances that conclusions drawn from results obtained by adding coloring matter or soluble salts are unreliable and in most cases open to suspicion. Kamerlingh Onnes held the view that the molecules of the impurity form attracting nuclei, which at the critical point cause rather disproportionate disturbances and modify profoundly the true critical phenomena. This opinion is entirely reasonable.

It seems perfectly clear then, that many of the abnormalities observed which affect the density greatly may be due to the effects of weight and impurities. If we deal with final states reached after stirring or long-continued heating, there is much evidence in favor of the classical theory of Andrews and van der Waals.

The experiments of a few years ago made by Callendar (3) on water and more recently the experimental evidence being accumulated by Professor Maass have reopened the question, and it now seems necessary to modify our ideas about matter in the critical region.

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CHANGES IN THE LIQUID STATE IN THE CRITICAL TEMPERATURE REGION[1]

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By a judiciously chosen sequence of temperature and pressure changes, the change of state from liquid to gas can be brought about in such a way that all physical properties, including that of density, vary continuously. Hence was developed the old classical theory of continuity of state, which postulates a similar structure or rather lack of structure for both gas and liquid. The results of a number of investigations which are to be described below cannot be explained on this basis. They tend rather to show that, quite apart from the question of concentration, a liquid has a structure (a dynamic structure) (10) to differentiate it from the static structure of a solid which a gas lacks. That does not mean that a continuous change from liquid to gas cannot be made to take place. For this to occur it is only necessary to assume that the change from structure to lack of structure occurs gradually under proper choice of pressure and temperature variation.

The use of the phrase "structure of a medium" implies of course a distribution involving certain regularities of its component parts. The component parts in the case of a liquid and vapor are assumed to be the molecules. In a gas these are in a completely chaotic random distribution and are free to move and rotate. In the case of a solid these gas molecules are regimented into perfect order and anchored into position. The classic theory based on the continuity of state had as its basis that the molecules in a liquid have the freedom of the gas molecules modified only by the enhancement of the forces of attraction due to greater proximity. To demonstrate that something more than this is required to explain the properties of liquids is the purpose of this paper, and it is hoped to make this evident by a review of the experiments carried out in the critical pressure–critical temperature region which are to be described.

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[1] A revised review of the subject matter presented at the Symposium on the Critical State, held by Section III of the Royal Society of Canada at Ottawa, Canada, on May 21, 1936.

The first of these experiments, and the one which gave rise to the series of critical temperature investigations in this laboratory, was the discovery that a certain reaction would take place in the liquid but not in the gaseous state. The particular reaction referred to is that between hydrogen chloride and propylene, where a homogeneous reaction occurs when the two reactants are compressed together to form a liquid medium, provided that this compression occurs below the critical temperature of the mixture. If the two substances, hydrogen chloride and propylene, are mixed as gases, heated above the critical temperature, and then compressed to a density equal to that of the liquid mixture below the critical temperature, the rate of the reaction at this temperature is less than at the lower temperature (18, 7).

Investigations were planned with the object of finding a possible explanation for this phenomenon, in particular, measurements of the P.V.T. relations of two-component systems in the critical temperature–critical pressure region. The experimental technique developed for the purpose was tested with a one-component system, and some unexpected results were obtained. It was found that a difference of density persisted between what had been the vapor and what had been the liquid above the temperature at which the visible meniscus disappeared (24, 19, 14).

After these observations had been made a survey of the literature showed that somewhat similar phenomena had been recorded before. I. Traube (21) and his collaborators, notably G. Teichner (20), showed that there was a density gradient in a tube containing a liquid and vapor heated above the critical temperature. Subsequent investigators ascribed their observations to inaccurate temperature control or to the presence of impurities. The consensus of opinion some six years ago is summed up very well by Jellinek, in his *Lehrbuch der Physikalischen Chemie* (8). He states that the results of Traube and coworkers are spurious and that in the "critical" region, where the compressibility is large, at most a gravitational effect might be expected, a suggestion first made by Guoy (5), i.e., density differences after meniscus disappearance, if not due to experimental error, can be assumed to be due to the compression caused by the weight of the medium itself.

The experimental technique developed in this laboratory made it possible to make precise density measurements in various parts of the medium above the critical temperature when kept under accurate temperature control. This not only permitted the verification of some of Traube's experimental conclusions, but also led to the discovery of other factors which are involved in this phenomenon.

It was found that when a liquid is heated above the critical temperature not only is there a difference in density above and below the point where the meniscus was last seen but there is a discontinuity in the density gradient at this point (24, 19). The magnitude of the density difference is dependent on the mass per volume relationship of the medium in the tube reaching a maximum when the tube is filled with an amount corresponding to the critical density as given by the Cailletet and Mathias rule. The density difference could not be destroyed by mechanical stirring, in which the lower medium was continuously carried throughout the upper part of the tube for 6 hr. (24). It was found that the difference in density persisted above the critical temperature with diminishing extent (as the temperature was increased), eventually reaching a zero value with continued rise in temperature. Some eight different substances have been investigated so far and the phenomenon found to be common to all these substances. The order of magnitude of the density difference above the so-called critical temperature varies from substance to substance, being[2] some 10 per cent for ethylene and 50 per cent for methyl chloride.

It may be emphasized that these density differences are equilibrium values in the sense that a final value is reached rapidly and then remains unaltered when the medium originally in the liquid–vapor state is heated up to the temperature at which density measurements are made. When the medium, after having been heated up to a considerable distance above the critical temperature, is cooled down these density differences are not reëstablished. This would look very much as if the density differences were perhaps merely the result of the persistence of a metastable condition.

Some weight is lent to this point of view by another observation. When the tube, in which a density difference persists above the critical temperature, is subjected to a temperature gradient in which the upper portion is kept at a lower temperature than the lower portion (sufficient to reverse the density difference and produce a circulation of medium), then, after bringing back the temperature of the medium to the original temperature, the density difference has been destroyed. Once destroyed it does not return spontaneously (24). The first inference is that the stirring induced by this procedure brought about this effect. However, the mechanical stirring mentioned above was shown to be effective in bringing about circulation throughout the tube and after 6 hr. did not even produce an indication of altering the density difference. Offhand it appears difficult to explain why a temperature gradient which produces stirring should destroy the density difference and mechanical stirring should not do so. Nevertheless an explanation will be attempted later on.

The data on which the above inferences are based were obtained by determinations in which no pressure measurements were made. The medium under investigation was confined in a fixed volume, and its pressure was governed solely by this volume and the temperature to which the medium was subjected. Resource was had to a technique whereby pressure could be both controlled and measured with a relative accuracy of 1 in 1000 at the critical pressure. As a result much more information of interest was collected in regard to the P.V.T. relationships of both one-phase and two-phase systems (10).

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[2] Just above the temperature where the visible meniscus disappears.

In the first place density isobars were determined, that is, the variation in density of the medium with temperature at constant pressure measured at pressures at and above the critical pressure (10). It was found that identical density values were obtained by approaching them first from a higher density (lower temperature) and then from a lower density (higher temperature). However, a real discovery was made, namely, that the time for establishment of equilibrium was very different depending on the direction of approach. The time for establishment of equilibrium was much greater with lowered temperature (increasing density) although, as mentioned before, exactly the same final values were reached (10).

This opened up a very fruitful field of investigation. The time for the establishment of thermal equilibrium was corrected for, and data were compiled in terms of "time to half-value." This was a purely arbitrary but convenient way of representing the time lag in establishing equilibrium. Final equilibrium values are reached asymptotically and, as the final equilibrium density values are known from the isobars, this is a useful and adequate method of comparing rates. In recording the time to half-value in establishment of equilibrium subsequent to temperature changes of ±0.02°C. along isobars the maximum was found to be at the steepest part of the isobar. The time to half-value in density changes from 0.158 in the case of ethylene to various final densities along four isobars made it evident again that the time required for equilibrium is greatest when the region in the isobar is approached which is the steep part of the isobar. When the medium is cooled down to a temperature where the liquid state exists, density equilibrium is established much more rapidly than when the medium is cooled down to the intermediate density of the isobar where rapid density changes take place. Time for the establishment of equilibrium in approaching densities on the steep part of the isobar (just above the critical pressure) becomes almost infinite when the approach is made from a low density. The general conclusion of a great number of experiments with isobars in the neighborhood of the critical temperature region is that equilibrium is established fairly rapidly when a rise in temperature or a decrease in density takes place, and very slowly when an increase in density or a lowering in temperature occurs. The longest time lags occur in the region of the isobars where great density changes take place. The higher the pressure the smaller is the time lag.

These experiments on time lag in the establishment of equilibrium are most readily explained on the basis that a liquid has a structure in the sense of certain ordered regularities in the distribution of the molecules. Rise in temperature would tend to destroy such a structure, depending on regularities in the arrangement of molecules due to increased kinetic energy of the molecules. Decrease in concentration would also tend to destroy the structure, owing to the increasing distance between molecules with resultant lessened mutual influence on one another. For a given temperature a critical concentration (i.e., density) can be envisaged where the structure begins to be disrupted. The form of the isobars can then be explained. When the critical density is reached a very small increase in kinetic energy of the molecules is sufficient to bring about a large expansion where the structure is on the point of being rapidly destroyed. The steep parts of the isobars, the points of inflection, are therefore the regions in which the liquid structure is disappearing. All time lag compilations are in direct agreement with this. Rise in temperature and consequent decrease in concentration (along an isobar) mean disruption of structure; the reverse means a building up of structure. If this is the case, longer times should be required for the establishment of equilibrium in the latter, if structure means anything involving orientation. At the points of inflection of the isobars the greatest changes take place in structure, and here are found the greatest time lags. If the production of an ordered arrangement on the basis of chance and probability takes a longer time to be established than its disruption, then the "time" experiments carried out may be explained if a liquid is assumed to have a structure.

The technique involving the simultaneous measurement of pressure and density, with results given later on, was also applied to the "two-phase system." This term "two-phase system" is used not only in the classical sense of starting with a system containing liquid and vapor but also for convenience in designating this system after the visible meniscus has disappeared and a density difference persists at the point where said meniscus vanished. Although actually data obtained with ethylene are made use of, figure 1 may be taken as typical of the change in density with temperature of the liquid phase of any one-component system in the critical temperature region. Curve A of figure 1 represents the density of a liquid and its variation with temperature right through T_c where the visible meniscus disappears.[3] After heating to *d* above the critical temperature, on subsequent cooling the density is constant (curve B) until at *e* the meniscus reappears, after which the density increases rapidly (curve C) with further lowering of temperature. But the equilibrium density of the freshly formed liquid is less than the density of the liquid while being heated up (at equal temperatures). All points on curves A, B, and C are reproducible and can be obtained time and time again. Curves B and C were always the same provided the medium had been heated up 5°C. or more above the critical temperature.

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[3] For convenience, the temperature at which the visible meniscus disappears when the two-phase system is heated up will be called *the* critical temperature.

It is convenient at this stage to consider the question of whether the density difference above the critical temperature could be due to the so-called gravitational effect (5) (i.e., due to the weight of the medium itself). One can see from figure 1 that there are density differences below the critical temperature (curves C and A) which from the continuity of the curves must be due to the same mechanism giving rise to the density differences above the critical temperature (curves B and A). The former can hardly be ascribed to the gravitational effect, hence the latter cannot either. It was always doubtful that the gravitational effect offered an adequate explanation, as it does not satisfactorily account for the sharp-

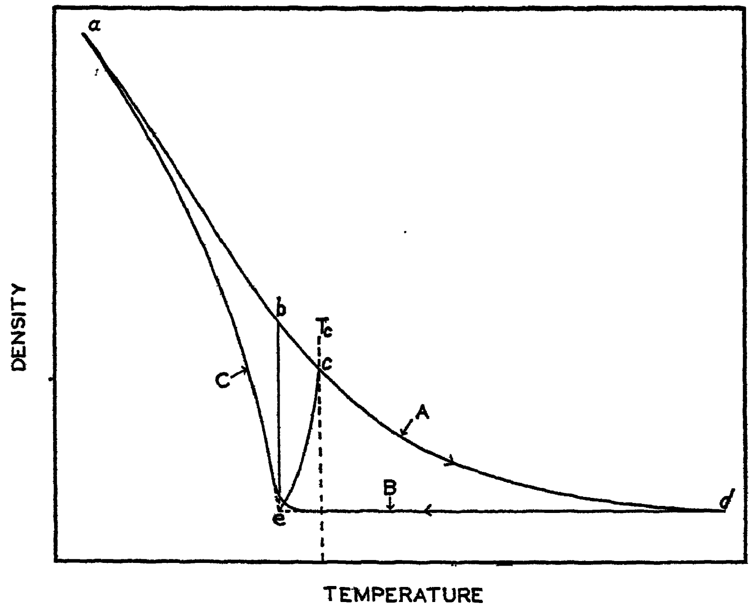

Fig. 1. Isochor (two-phase system). Curve A: variation of density of liquid with rising temperature (*ac*); *c*, critical temperature; *cd*, variation of density of medium below disappearance of meniscus with rise in temperature; *d*, disappearance of density difference. Curve B: *de*, density of medium with rise in temperature; *e*, reappearance of meniscus. Curve C: variation of density of liquid with rise in temperature.

ness of the density discontinuity (24) nor for the fact that, once destroyed, the density differences are not reëstablished by cooling or compressing the medium. Furthermore, when pressures could be accurately measured the compressibility of the medium under the density and temperature conditions was evaluated. The pressure caused by the weight of the whole medium was estimated to be only one-twentieth of that necessary to cause observed density differences, and these differences would be spread continuously between the top and bottom of the tube containing the medium and not in the narrow region within which the abrupt density changes are observed to occur. It is not disputed that there is a density gradient due to gravity superimposed on the density discontinuities, but these are of an inferior order of magnitude. Consequently the density differences must be explained otherwise, most readily on the basis of the persistence of the liquid state of aggregation with a structure above the so-called critical temperature.

It was believed to be of interest to see what would happen when temperature lowering was carried out before the (two-phase) medium had been heated up to the temperature where density differences had disappeared, and also to see what would happen to the density of the liquid formed along curve C (figure 1) when again heated. It was found that in the former case the new density curve lies below curve A and in the latter above curve B. Apparently any density in the area enclosed by curves A, B, and C can be obtained, and once obtained holds indefinitely as long as the temperature remains constant, i.e., no spontaneous change occurs subsequently.

All this can again be explained tentatively on the basis that a rise in temperature brings about a disruption of structure, which takes place rapidly, while a lowering in temperature tends to bring about a building up of a structure, which takes place slowly, and under certain temperature and pressure conditions takes place infinitely slowly. When the isochors of the two-phase system are plotted with the isobars (figure 2)[4] of the one-phase system, it is seen that the densities of the two-phase system lie on the steep parts (points of inflection of the isobars) where temperature or concentration changes tending to bring about a building up of structure take place almost infinitely slowly, as was mentioned before.

Another way in which any density in the region enclosed by curves A, B, and C can be attained by experimental manipulation has suggested an explanation of the mystery of the elimination of density differences by the temperature gradient mentioned before. This manipulation may conveniently be called "temperature fluctuations." Suppose one starts with the (two-phase) medium under a condition represented by some point on curve A and then subjects it to a slight cooling followed by a slight warming, oscillating the temperature changes around the original temperature; then the density changes found to take place are as follows: The density approaches the lower value for the mean temperature on curves B or C. Any time the fluctuations are stopped and the temperature kept constant, the density remains unchanged. It is possible to see why these results are obtained. On heating structure is presumably destroyed; on cooling it is not restored, owing to the greater time lag. It is evident then why the temperature gradient,—top cold, bottom hot,—destroys the density difference of the two-phase system above the critical temperature. It is not the stirring produced which does it, because mechanical stirring at uniform temperature does no such thing; it is a fact that the medium is subjected to alternate cooling and heating, and this is equivalent to a case of "temperature fluctuations."

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[4] Typical of any one-component system.

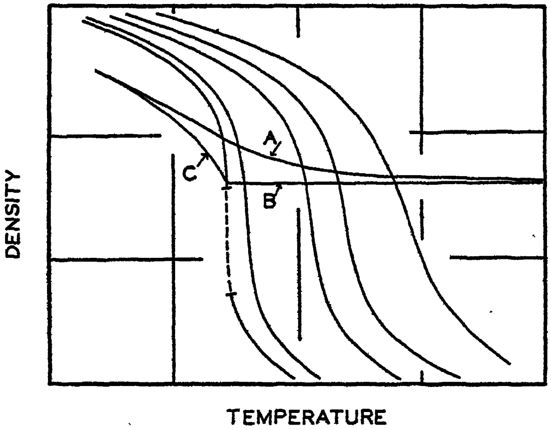

FIG. 2. Relation of isochor representing two-phase system to isobars representing one-phase systems.

In a series of experiments the two-phase system above the critical temperature was subjected to expansion and contraction. It was found that the density difference was destroyed both by expansion and by compression. Consequently in this connection it may be predicted that violent stirring such as would be produced by a rotating propeller may well bring about the same results. Such a mechanism would bring about local expansions and contractions. In the stirring previously mentioned the lower medium was continuously lifted up into the upper portion of the tube, subsequently streaming down and visibly giving a thorough stirring. This, however, was evidently accomplished without local expansion and contraction, so that after 6 hr. of such stirring the original density difference remained unchanged.

The question of the relative stability of the system as represented by curves A, B, and C of figure 1 is pertinent. Without temperature or volume fluctuations any density represented within the area enclosed by the curves A, B, and C persisted unchanged as long as measurements could be made. It was found that the density indicated by any point on curve A is gradually reduced by a process of temperature fluctuations or isothermal compressions and expansions, whereas the reverse process does not occur when starting at any point on curves B and C. This would appear to be indicative that these latter represent "the stable condition." However, it has been shown that in the critical region equilibrium is quite rapidly established when the temperature is changed in the direction of decreasing density and all it implies, whereas the time lag involved in an increase in density may be immeasurably slow. Hence, temperature fluctuations about a mean value would produce a continued decrease in density until curve B was reached. The decrease in density due to temperature fluctuations may thus be explained on the basis of a time factor and does not imply with certainty that the lower curves represent the stable condition.

The results obtained from pressure measurements on curves A, B, and C made with an accuracy of 0.005 atm. (10) do not give a conclusive answer as to the relative stability of the two curves. The results indicate that below the critical temperature the pressure on curve A is just measurably greater than that on curve C at the same temperature, since it was possible to obtain reproducibly a difference in pressure of 0.01 atm. Above the critical temperature the difference in pressure was only half that found in the previous case and was in the opposite direction. However, as the pressure measurements depended on the reproducibility of the volume of the medium as well as on the accuracy of the pressure measurements themselves, the difference must be considered as being within the limit of experimental error. From this evidence it may be inferred that the stability of the system when corresponding to points on curves A, B, or C at the same temperature or any intermediate points is very nearly the same.

When a liquid is heated in equilibrium with its vapor the density of the liquid gradually decreases. Let us assume that the liquid has a structure. Both rise in temperature and decrease in concentration tend to break up this structure; a point is reached where a critical concentration is approached, "critical" in the sense that the structure of the liquid breaks down rapidly accelerating the decrease in density. For a given temperature above this point there are two limiting concentrations between which the structure rapidly decreases, and a rapid decrease in cohesive force takes place proportional to the decrease in concentration. Now the vapor pressure exerted by a liquid at a given temperature may be roughly put as being *directly* proportional to concentration in the liquid and *inversely* proportional to cohesive force existing in it. That is, it is proportional to concentration on one count and inversely proportional to concentration on another count. In the concentration (i.e., density) region, where cohesive force is proportional to concentration, the pressure is constant, i.e., the liquid can have various densities and exert the same vapor pressure. The above is of course in the nature of an approximation and is not to be taken as a quantitative representation. It gives the picture that in the critical temperature region the liquid can have a range of densities in which it will exert the same pressure. This also offers an explanation of the density discontinuities existing above the temperature at which the visible meniscus disappears, the latter being simply the temperature where the meniscus, i.e., change in density from liquid to vapor, is not abrupt enough to be visible.

Investigations other than density measurements have been published which indicate that a difference of property persists in a medium above and below the disappearance of the meniscus. These involved adsorption measurements (15, 3), surface tension measurements (23), and dielectric constant measurements (11, 12).

Apart from these, heat capacity measurements have been made which show that there is a measurable difference in the heat capacity when the system is under conditions represented by A and by B and C (figure 1) (1). Viscosity measurements are now under way (13). The influence on curves A, B, and C due to the presence of traces and of appreciable amounts of inert gases has given results which confirm the persistence of a liquid state having structure above the critical temperature (14). All this will be published shortly.

The object of presenting the above review is to indicate that measurements in the critical temperature–critical pressure region are of interest, inasmuch as the results obtained may help to evolve a hypothesis of the liquid state of aggregation.

The idea that the writer originally had, namely, that structure was in the nature of regional orientation, can be expressed by the following quotation written some fourteen years ago: "The distinction between regional orientation and a small crystal is that all the atoms in a small crystal may be looked upon as belonging to the same molecule, whereas in a region where orientation has taken place the molecules retain their identity and have translatory and rotational energy possessing only an averaged orientation for a time. The regions in a liquid are not sharply defined, but pass gradually and without any discontinuity into one another. These regions may be momentarily represented by arrows giving the direction of orientation. Contour lines around these arrows would represent the gradual diminution of orientation and blending with the direction of a neighboring region. These contour lines would be continuously shifting, orientation arrows disappearing and new ones appearing in fresh places" (9).

Stewart (16, 17) has developed somewhat similar ideas under the name of "cybotactic groups" to explain his interesting investigation of x-ray diffraction patterns of liquids.

At this stage the writer is convinced only of a few generalities. These are as follows: (*1*) that a liquid has a structure due to certain regularities of molecular distribution in a liquid which are not in the nature of association of molecules; (*2*) that the structure is a dynamic one; (*3*) that rise in temperature and decrease in concentration tend to destroy structure, a change which may be described as a tendency of the liquid state of aggregation to turn into the gaseous state of aggregation; (*4*) that what has been called the critical temperature is the temperature at which the normal density of a liquid has decreased to a point beyond which structure rapidly diminishes; (*5*) that the liquid state of aggregation can exist above this temperature when the density of the medium is increased by pressure sufficient to bring about a necessary concentration.

The interest in the nature of liquids is widespread, and among others Debye (2), Warren (22), Eyring (4), and Mayer and Harrison (6) have presented novel and valuable theories.

Mayer and Harrison, by the application of statistical mechanics to condensing systems, have arrived at certain conclusions in regard to the properties of a medium in the critical temperature region which are in striking agreement with the experimental results obtained in this laboratory. Some experiments recently carried out to test certain predictions made by Mayer and Harrison have fully confirmed these predictions.

In conclusion it may be reiterated that experiments carried out in the critical temperature–critical pressure region, where the change from liquid to gas is most pronounced, should be a deciding factor in leading to a final answer as to the nature of the liquid state of aggregation.

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THE DIFFRACTION OF X-RAYS BY SUBSTANCES IN THE REGION OF THE CRITICAL POINT[1]

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INTRODUCTION

Before considering the data at present available on the diffraction of x-rays by substances in the region of the critical point, it is appropriate to review briefly the salient features of the scattering of x-rays by gases and by liquids under conditions not approaching the critical. It is the object of this paper, therefore, to present a brief review[2] of such x-ray data for gases, liquids, and fluids in the critical region, and to consider the generally accepted theories designed to account for the observed effects, in the hope that this review will be of value particularly to those whose chief interests do not lie in the field of x-ray analysis but who are interested in all phenomena associated with the critical state.

GASES

The most characteristic feature of the scattering of x-rays by gases is the relatively high intensity exhibited at small angles from the direction of the incident beam. Typical intensity curves (reference 17, pages 55 and 69) are reproduced in figure 1a for a monatomic gas (argon) and in figure 1b for a polyatomic gas (carbon tetrachloride), respectively. Without going into details the scattering of x-rays by gases has been satisfactorily explained, largely by Debye, from the following considerations. The intensity of the scattered radiation and its variation with angle depend on the electronic structure of the atoms concerned and, in polyatomic gases, on the relative arrangements and relative sizes of the atoms in the molecules. The undulatory nature of the curves for polyatomic gases is introduced by the molecular structure. Since the molecules in a gas are separated by comparatively large distances and are characterized by a random distribution and orientation in space, the observed effects are due solely to interference phenomena among waves scattered by the atoms within the molecules. There is no resultant effect of interference among waves scattered from neighboring molecules. The observed effects, therefore, are intramolecular. Intermolecular interference is negligible. Satisfactory quantitative agreement exists between intensities calculated from

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[1] A review presented at the Symposium on the Critical State, held by Section III of the Royal Society of Canada at Ottawa, Canada, on May 21, 1936.

[2] In the preparation of this paper valuable assistance has been derived from Randall's treatise (17), from Wollan's excellent review of "X-ray Scattering and Atomic Structure" (28), and from the papers cited at the end of this review. Figures 1, 2, and 5 are reproduced from Mr. J. T. Randall's book (17) with the kind permission of the author and the publishers. Grateful acknowledgment is also made to Dr. B. E. Warren for permission to use figures 3 and 7, to Professor G. W. Stewart for figures 4 and 6, and to Dr. G. G. Harvey for figure 8.

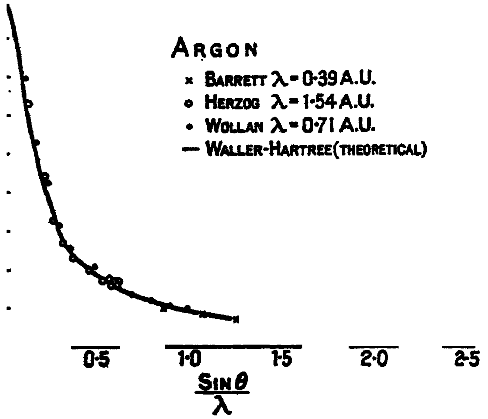

FIG. 1a. X-ray scattering curve for argon (from Randall (17) after Wollan (28))

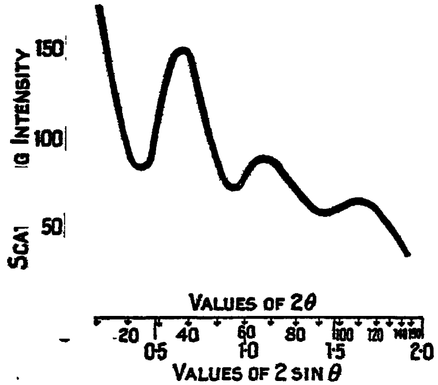

FIG. 1b. X-ray scattering curve for carbon tetrachloride (from Randall (17) after Debye)

equations based on these conceptions and experimentally observed data. Wollan's review (28) should be consulted for further details.

LIQUIDS

The scattering of x-rays by liquids resembles that by solids much more closely than it does that by gases. There is no doubt that the observed effects are due both to intermolecular and to intramolecular interference. It has frequently been shown, as for example in figure 2 (reference 17, page 116), that the observed intensity curves for liquids closely resemble smoothed-out, diffused curves for the corresponding crystalline solids. A liquid, therefore, appears to possess a "structure," as distinct from the chaos characteristic of a gas. The very nature of a liquid, however, precludes any idea of the comparatively rigid structure obtaining in a crystal. O. Maass has proposed the rather apt term "dynamic structure" to distinguish the condition of the liquid from what he calls the "static structure" of the crystal.

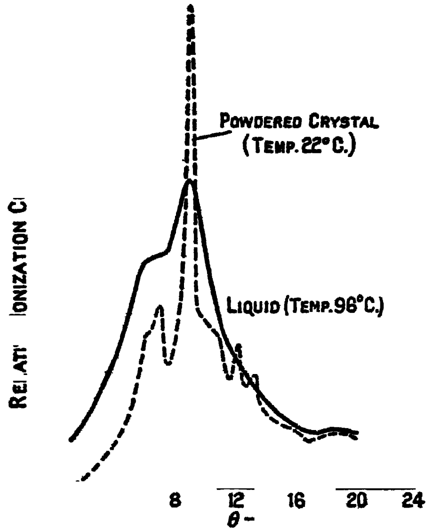

FIG. 2

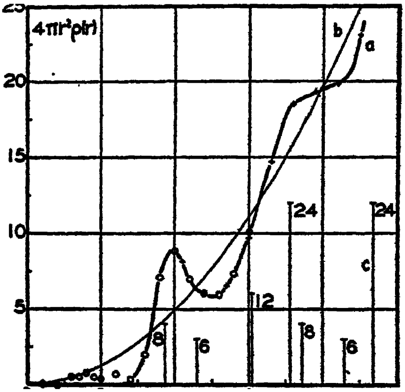

FIG. 3

FIG. 2. X-ray diffraction curves for equal masses of liquid and powdered triphenylmethane (from Randall (17) after Stewart (19)).

FIG. 3. a, radial distribution curve for liquid sodium; b, average density curve for liquid sodium; c, distribution of neighbors in crystalline sodium (Tarasov and Warren (24)).

Apart from an attempt by Raman and Ramanathan to account for the scattering of x-rays by liquids in terms of the Smoluchowski–Einstein treatment of the scattering of visible light, the most important, and at present generally accepted, methods of considering the x-ray data are due to Zernike and Prins, Debye, and Stewart. Zernike and Prins and Debye have approached the problem mathematically, while Stewart has explained the effects descriptively.

The viewpoint of Zernike and Prins and of Debye is that of an essentially homogeneous liquid possessing a "structure" which may be represented by means of a calculable distribution function. The distribution of atoms or molecules throughout the liquid resembles that in the crystal but is, of course, much more mobile. Zernike and Prins evaluate the distribution function empirically and compare intensities calculated therefrom with observed data. The distribution function may then be adjusted until reasonable agreement with experimental results is obtained. Debye calculates the distribution function directly from the experimental data and thus obtains a *probable* distribution. Among the more recent applications of these methods to specific problems may be mentioned the work of Bernal and Fowler (3) on the "structure" of water, of Katzoff (9) on water and certain organic liquids, and of Tarasov and Warren (24) on liquid sodium. Reference to these papers[3] will illustrate the type of calculations involved. Figure 3 (from the paper of Tarasov and Warren (24)) shows (*a*) the average density of sodium atoms surrounding a given atom (given by $4\pi r^2\rho(r)$, where $4\pi r^2\rho(r)\,dr$ is the number of atoms between distances r and $r + dr$), (*b*) the average density curve (given by $4\pi r^2\rho_0$, where ρ_0 is the average density of the sample in atoms per unit volume), and (*c*) numbered ordinates representing the distribution of neighbors in crystalline sodium.[4] As Tarasov and Warren (24) point out, "It is very evident that the density curve of the liquid [curve (a)] is essentially a smoothed out distribution curve for the crystalline phase." The last paragraph of their paper (24) is pertinent to the present review and is worth quoting *verbatim et literatim.* "The density curve . . . [Fig. 3 (a)] . . . represents the 'structure' of liquid sodium as specifically as this quantity can be represented. It should perhaps be emphasized that this curve is obtained directly from the experimental x-ray curve, without making any *a priori* assumptions as to the atomic arrangement in the liquid. It is evident that there is such a thing as a 'structure' in a liquid, a structure which has to do with the average distribution of neighboring atoms about any one atom. There appears to be no necessity for postulating a crystalline type of structure[5] in the liquid, to explain a distribution curve such as . . . [Figure 3]."

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[3] See also "A General Discussion on Structure and Molecular Forces in (a) Pure Liquids and (b) Solutions," Trans. Faraday Soc. **33**, 1–282 (1937), particularly pp. 27–45, 105–9, 110–12.

[4] The ordinate, numbered 6, at $r = 4.6$ should appear at $r = 4.3$, according to a private communication from Dr. Warren. There is also an error of about 2.5 per cent in the scale of abscissae for curve *a* (radial distribution curve), so that all distances read from figure 3a should be 2.5 per cent smaller (Warren: J. Applied Phys. **8**, 651 (1937)).

G. W. Stewart employs a qualitatively descriptive method to explain the observed scattering phenomena. He considers the liquid to be composed of regions in which the molecules possess mutual orientation separated by regions in which the molecules are distributed in a completely random manner as in a gas. This condition is termed "cybotaxis" and the orderly regions of molecular aggregates are called "cybotactic groups." The viewpoint is similar to that embodied in Maass' conception of "regional orientation" (10).

In a recent paper from Stewart's laboratory Spangler (18) has presented the following summary of the "cybotactic" view and of the essential difference between it and that of Zernicke, Prins, and Debye. "It is generally known that liquids show a structure simulating, but by no means approaching, that found in crystals. There are at least two views as to the nature of this 'liquid structure.' One is illustrated by computations, based on a homogeneous conception of a liquid. . . . Another is that the liquid is non-homogeneous but, at any instant, there are enough molecules in groups, simulating crystalline structure, called cybotactic groups, to indicate this temporary and vacillating structure when investigated by x-rays. These groups do not have definite boundaries but are temporary regions of orderliness shading off into regions of little orderliness. The former view is quantitatively successful in matching the experimental curves. The latter view is not so easily subjected to mathematical treatment and is content to point out the simulation of crystal structure for which the theory is well known. Both views are approximate, the former adjusting the view to the theory then to be applied and the latter using the crystal theory already established as an approximate guide to an understanding as to what occurs within the liquid."

Stewart (19, 21) suggests that the cybotactic groups may comprise from twenty-five or fifty to one thousand molecules each, "that they are not perfectly regular, that there is a fluctuating density in the liquid, and that the shape of the molecules cannot be considered as constant" (reference 19, page 985). At ordinary temperatures he estimates that "the percentage of molecules not in such groups at any instant is small. For example, in the case of ethyl ether at room temperature it appears that perhaps 7 to 10 per cent of the molecules scatter x-rays as would a gas" (reference 19, page 988). It is of interest to note in passing that Stewart considers "liquid crystals" to be composed of aggregates of modified cybotactic groups containing something of the order of 10^6 to 10^9 molecules each (19, 21).

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[5] "By a *crystalline structure* one means an array of atoms in which some unit of structure repeats itself identically at regular intervals in three dimensions. In using terms such as 'structure' it is necessary to state precisely whether crystalline structure is meant, or whether the term is being used in a more general sense" (Tarasov and Warren).

In general the scattering of x-rays by liquids differs from that by gases in the much lower intensities exhibited at small angles (compare figures 1 and 2). It is with this small angle scattering (i.e., within about 15°) that the following section is concerned.

FLUIDS IN THE REGION OF THE CRITICAL POINT

Although the number of substances which have been subjected to x-ray examination in the critical region is at present very limited, the results that have been obtained to date are of very great interest and give promise of important developments in the future. In the laboratory of G. W. Stewart, Noll (16) and Spangler (18) have investigated the scattering of x-rays by ethyl ether, and Benz and Stewart (1) have studied the effects from isopentane. Elsewhere Harvey (8) has obtained some important results from nitrogen at high pressures, and Gingrich and Warren (7) have considered the mathematical problem of interpreting the scattering of x-rays by a fluid at high densities with a modification of the methods of Zernike and Prins.

Typical experimental results obtained by Spangler (18) and by Benz and Stewart (1) are shown in figures 4, 5, and 6. For reference purposes the critical constants of ethyl ether are as follows: T_c, 194.6°C.; P_c, 36.7 kg. per square centimeter; V_c, 3.77 cc. per gram; and for isopentane T_c, 187.8°C.; P_c, 33.9 kg. per square centimeter; V_c, 4.2 cc. per gram (18, 1).

Figure 4 for isopentane at a constant pressure above P_c shows the effect of increasing temperatures and specific volumes (1). As the temperature and the specific volume increase, the scattering intensity curve characteristic of a liquid exhibited at temperatures and specific volumes considerably below the critical (curve 1) changes gradually and continuously into that characteristic of a gas exhibited at temperatures and specific volumes considerably above the critical (curve 9). The same trend appears in similar sets of curves for ethyl ether and isopentane at various constant pressures, the peak in the curve characteristic of a "liquid structure" disappearing at high temperatures and specific volumes. Of particular importance is the fact that at constant pressures above P_c the "liquid structure" (i.e., a peak in the intensity curve) persists *above* T_c and V_c in both isopentane and ethyl ether. This will be referred to again later.

At a constant temperature (above T_c) the peak diminishes and disappears with increasing specific volume and decreasing pressure (figure 5 (18; 17, page 169)).

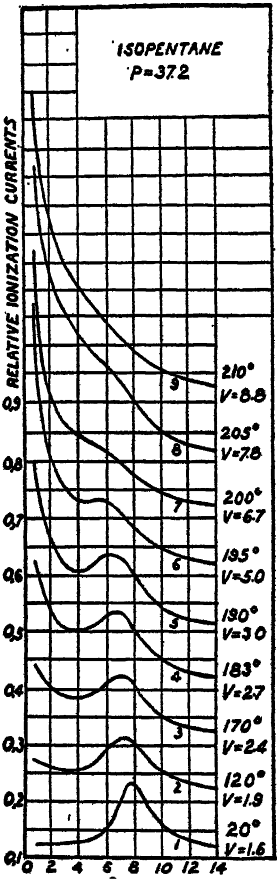

FIG. 4

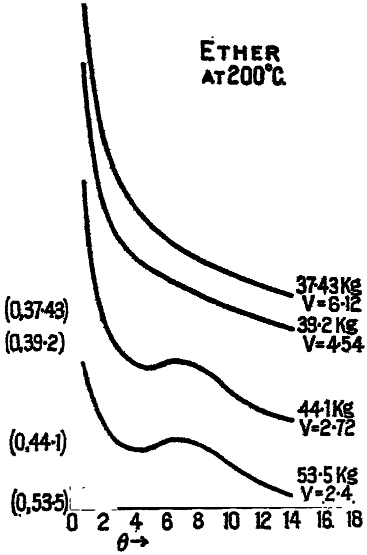

FIG. 5

FIG. 4. X-ray scattering curves for isopentane at a constant pressure of 37.2 kg. per square centimeter (Benz and Stewart (1)).

FIG. 5. X-ray scattering curves for ethyl ether at a constant temperature of 200°C. (from Randall (17) after Spangler (18) and Stewart (19)).

On the other hand, at constant specific volume (above or below V_c) no significant change occurs in the appearance of the curves with change in temperature and pressure (figure 6 (18)). As Spangler (18) points out, this behavior is unique because a variation along any line of the P–V–T diagram with the sole exception of an isometric produces a marked change in the scattering phenomena observed.

With both ethyl ether and isopentane the persistence of a "structure" above the critical pressure depends most importantly on specific volume and not on the critical temperature. With either fluid above the critical pressure, decreasing the specific volume results in a more pronounced peak in the intensity curve.

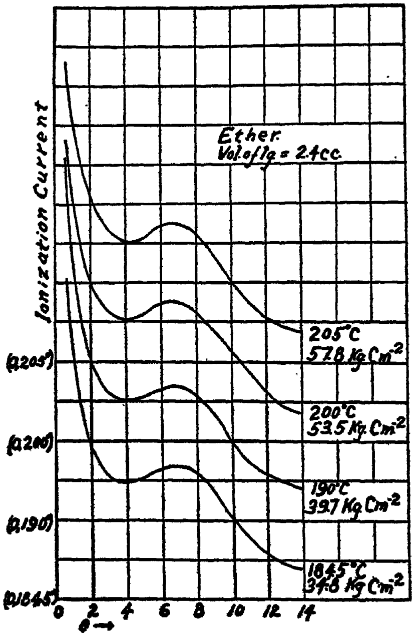

FIG. 6a

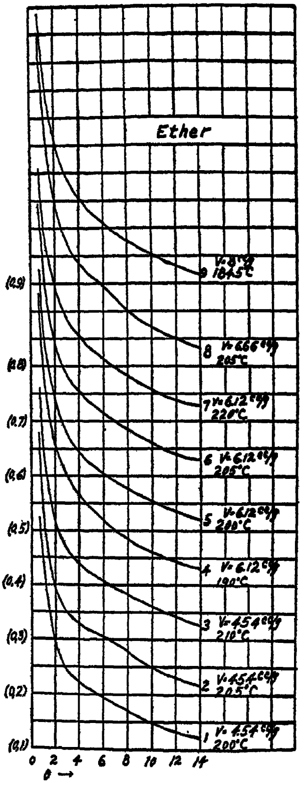

FIG. 6b

FIG. 6a. X-ray scattering curves for ethyl ether at a constant specific volume of 2.4 cc. per gram (Spangler (18)).

FIG. 6b. X-ray scattering curves for ethyl ether at specific volumes greater than 4 cc. per gram (Spangler (18)).

Benz and Stewart (1) point out that the most striking difference between the results for ethyl ether and those for isopentane is that the "liquid structure" persists to a specific volume much larger (by about 90 per cent) than V_c in the case of isopentane, whereas it disappears at about the critical volume in the case of ethyl ether. This is somewhat surprising since isopentane has no measurable dipole moment, whereas ethyl ether is definitely polar. Benz and Stewart (1) conclude, therefore, that "the forces arising from polarity seem to be of minor importance in the comparison of the two liquids or in a consideration of the molecular forces."

Spangler (18) and Benz and Stewart (1) explain their results in terms of the cybotactic groups previously mentioned. They consider that, at least "for purposes of discussion, . . . one may regard the disappearance of the typical liquid peaks as the vanishing of any marked cybotaxis" (reference 1, page 706) and "the presence of peaks, with or without gaseous diffraction (i.e., high intensities at very small angles, e.g., the first portions of the intermediate curves in figure 4), is assumed to indicate the formation of some cybotactic groups, the incipient ones, of course, not being in size or structure alike throughout the experiments" (reference 1, page 703). The dependence of the peaks on specific volume is considered to arise from the operation of molecular forces. Since these forces "undoubtedly vary rapidly with the distance of separation of the molecules" (reference 18, page 702), peaks should be present in all curves for specific volumes less than a certain value (characteristic of the substance concerned and not necessarily equal to V_c), whereas at higher specific volumes typical "gas" curves should be obtained the general character of which should be independent of temperature, pressure, and volume (e.g., compare figure 6a and figure 6b). As Spangler says, "This corresponds to the view that, after a certain distance of separation of the molecules has been obtained, the molecular forces are no longer effective in producing orderliness among the molecules" (reference 18, page 702). A careful examination of the various curves in the papers of Spangler (18) and Benz and Stewart (1) shows that they may all be explained satisfactorily in terms of "cybotactic groups," or "regional orientation" of molecules, and changes in size or regularity which such groups, or regions, might be expected to undergo under changing conditions.

Insofar as the x-ray data alone are concerned Gingrich and Warren (7) and Harvey (8) have shown that the hypothesis of "cybotaxis" or "regional orientation" is not essential for the interpretation of the observed scattering of x-rays by fluids at relatively high densities.

Gingrich and Warren (7) have employed a modification of the method of Zernike and Prins by deriving a more suitable equation for the intensity which involves a distribution function more in accord with the density distribution to be expected from Morse's potential energy curves (15). For a monatomic gas the density distribution is such that about any one atom there are no atoms closer than a certain minimum distance; there is a slight concentration of atoms at this distance, after which the density rapidly becomes constant. For a liquid with approximately close-packed atoms there is the same minimum distance of closest approach, a marked concentration at this distance with a corresponding deficiency just beyond, after which the density distribution curve oscillates about the average density a few times before becoming constant. By suitable and reasonable adjustment of certain factors in the intensity equation Gingrich and Warren (7) have been able to construct curves for ethyl ether at various densities (figure 7) which are in very satisfactory agreement with those obtained experimentally by Spangler (18).

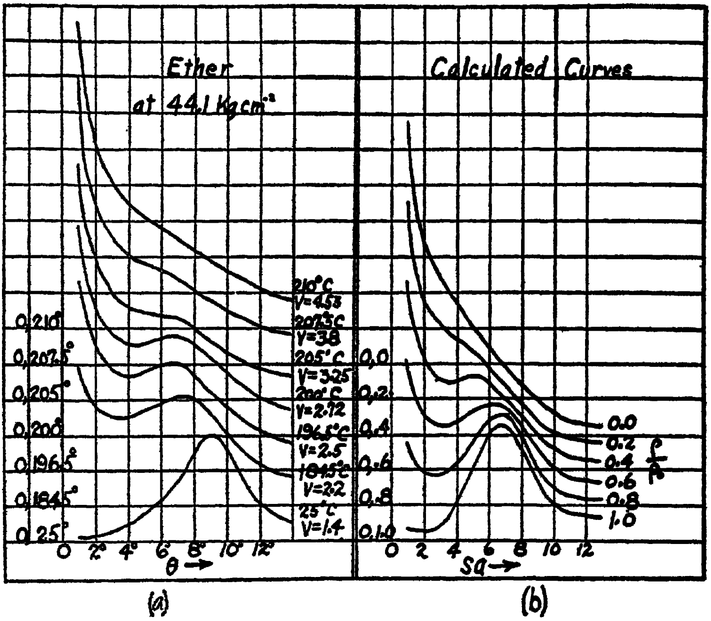

FIG. 7. X-ray scattering curves for ethyl ether at a constant pressure of 44.1 kg. per square centimeter. a, observed (after Spangler (18)); b, calculated (Gingrich and Warren (7)).

Harvey (8) has measured the intensities of x-rays scattered at angles less than about 10° from nitrogen at pressures corresponding to 60, 80, and 100 atm. at 0°C. A pronounced peak in the curve was obtained in each instance (figure 8). The critical constants for nitrogen are given in the International Critical Tables[6] as P_c, 33.5 atm.; T_c, −147.1°C.; d_c,

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[6] Volume III, page 248.

0.311 g. cm.$^{-3}$. The pressures employed by Harvey, therefore, were all greater than P_c. Harvey shows that his experimental values are in good agreement with theoretical curves based on Debye's equation for a diatomic gas. This assumes no molecules closer to a given molecule than the diameter of the molecular sphere of influence and a uniform density distribution thereafter. Harvey, therefore, concludes, with Gingrich and Warren (7), that the "decrease in scattering at small angles is due merely to the fact that there are a large number of scattering centers within a small space, rather than to any preferred grouping of the molecules, since the existence of such groups would be very unlikely in a gas so far from the liquid state" (reference 8, page 445).

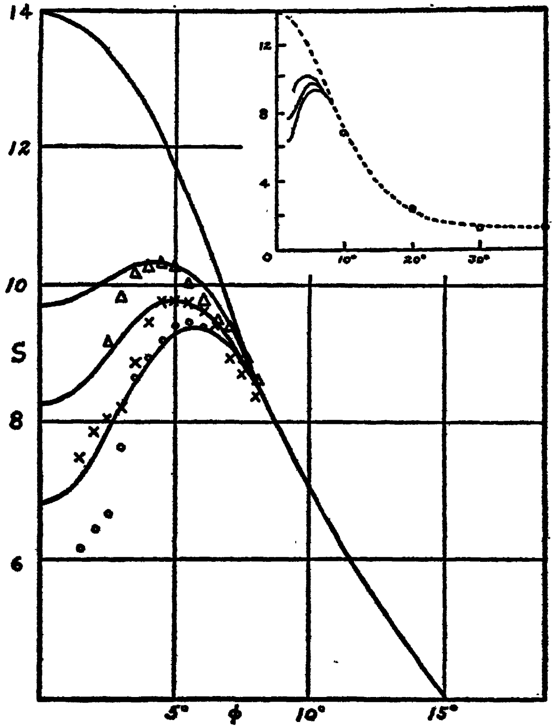

FIG. 8. X-ray scattering curves for nitrogen. Solid curves according to Debye's theory for 0, 60, 80, and 100 atm. Experimental points: △, 60 atm.; ×, 80 atm;. ○, 100 atm. (Harvey (8)).

DISCUSSION

It has already been emphasized by Bernal (2) and by Stewart (20) that x-ray scattering data alone are insufficient to determine the "structure" of a liquid uniquely. This fact is brought out forcibly by the satisfactory nature of each of the two different points of view at present utilized for the interpretation of the x-ray results,—namely, the mathematical treatment in terms of the distribution of the molecules in a liquid with, or without, a non-uniform density distribution, and the qualitative description of the liquid state in terms of cybotactic groups or regional orientation of molecules. From either of these viewpoints a liquid possesses a "structure," whether it be due simply to an optimum distribution of molecules due to their relatively close proximity to each other, or whether it consists of transitory regions of semi-order merging into and separated by regions of completely random orientation. Furthermore, there is strong evidence for the continued existence of such a "structure" above the critical point as normally defined.

The results of a series of physicochemical investigations by A. L. Clark (5) and, during the past few years, by O. Maass and his coworkers (12, 22, 27, 23, 14, 6, 13, 11) on fluids in the region of the critical point have shown that the assumption of a "liquid structure" and its persistence under certain conditions above the critical temperature is necessary to account for the data obtained. For example, among the interesting facts which have emerged from Maass' investigations are the following: When ethylene, dimethyl ether, or propylene is heated above T_c a difference in density between the regions above and below that where the meniscus disappears persists to temperatures considerably above T_c. This has been shown not to be due to a gravitational or temperature gradient effect. Furthermore, when the gas is cooled from very high temperatures where a uniform density exists, no density difference is reëstablished until the meniscus reappears. These results indicate that a "liquid structure" persists above T_c when the approach is from lower temperatures, but that when the approach is from a higher temperature this "structure" does not become evident until an appreciably lower temperature is reached than that at which the "structure" previously was broken up. This is in agreement with the well-known fact that it is more difficult to establish order in a system than it is to create chaos. It has also been shown that the time required to establish equilibrium in the critical region along an isobar is greater when a point is approached from high temperatures than it is when the fluid is initially at lower temperatures. Other results have shown that a marked difference in the dielectric constants of fluids between the liquid and vapor regions persists above the critical temperature and follows the density differences mentioned above. Further evidence for the persistence of the "liquid structure" is to be found in the shape of the sorption curves for dimethyl ether and propylene, respectively, on alumina. For further details reference should be made to the original papers (12, 22, 27, 23, 14, 6, 13, 11).

A density difference above the critical temperature has also been observed by Traube (26) and Teichner (25), and H. L. Callendar (4) has presented strong evidence for a discontinuity of state above T_c in the case of water–steam. For example, on the total heat versus pressure diagram the steam saturation line does not coincide with the water saturation line, and on the density versus temperature curves the water density curve does not meet the steam density curve, until a temperature of about 380.5°C. is reached in each case, whereas T_c is equal to 374°C.

The x-ray data, therefore, are in agreement with physicochemical evidence that a liquid must possess a "structure" as distinct from the state of disorder characteristic of a gas. At the present time the two theories which appear to be in best agreement with the various observations available are those already outlined. The fact that the observed scattering of x-rays by fluids in the critical region can be accounted for satisfactorily in terms of the possible distribution of molecules relative to one another does not automatically preclude preferred orientation of molecules in more or less discrete regions. The results of Harvey (8) on nitrogen constitute the only positive experimental evidence apparently against the conception of cybotactic groups being necessary to produce the x-ray scattering observed. Further experiments on other gases at high pressures but at temperatures far removed from T_c, therefore, are urgently needed. On the other hand the results from Maass' laboratory, particularly those on densities and on the times required for equilibrium conditions to be established, are very difficult to understand from the point of view of a mere distribution function without any orientation factor. These results would seem to be more reasonable if the appearance and disappearance of a "liquid structure" involved not only a disintegration and formation of a preferred coördination number of molecules but, in addition, the disruption and reformation of groups having a mutually established direction of preferred orientation.

More x-ray data are required on other substances in the region of the critical point. Of particular interest would be the correlation of data on the scattering of x-rays by ethylene, propylene, and dimethyl ether with the results of Maass' investigations. These three substances have critical constants apparently suitable for the application of the technique and type of apparatus developed by Stewart. Their polarity increases in the order named, and in view of the results on ethyl ether (18) and isopentane (1) a systematic study of substances with various dipole moments would be of great importance. It would be interesting to know whether the prolonged persistence of the "liquid structure" in isopentane as compared to ethyl ether is due perhaps to a peculiarity of the molecules concerned or whether it is really caused by the suggested lack of importance of polarity as a factor influencing the "liquid structure." If the latter suggestion is substantiated, then regional orientation presumably would involve the operation of non-uniform van der Waals forces.

In view of the density hysteresis effect observed in Maass' experiments an exceedingly interesting study could be made of the scattering of x-rays by ethylene at various temperatures approaching and passing the critical temperature and then at corresponding temperatures in the reverse order.

In conclusion, therefore, it is evident that liquids do possess a "structure" which persists under certain conditions above the critical temperature. This "structure" may consist simply of a preferential distribution of molecules throughout the fluid or of regions of preferred distribution and orientation. The results of Harvey favor the former view, the results of Clark and of Maass favor the latter. Interesting developments, therefore, may be expected in the future from further physicochemical investigations and from a more extended and directed examination of the diffraction of x-rays by substances in the region of the critical point.

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SYMPOSIUM ON THE LESS FAMILIAR ELEMENTS

In addition to the papers printed in this Journal[1] the program of the Second Annual Symposium of the Division of Physical and Inorganic Chemistry of the American Chemical Society on "The Less Familiar Elements," held at Cleveland, Ohio, December 27, 28, and 29, 1937, contained the following papers. References are given for such of these papers as have been published; for some others the probable medium of publication is listed.

General Introduction to the Symposium. H. S. Booth, Western Reserve University, Cleveland, Ohio.

The Non-terrestrial Occurrence of the Less Familiar Elements. J. Papish, Cornell University, Ithaca, New York.

Occurrence of the Less Familiar Elements in Everyday Materials. B. F. Scribner, National Bureau of Standards, Washington, D. C. (Probably to be published in *Industrial and Engineering Chemistry, Analytical Edition.*)

Economics of Some of the Less Familiar Elements. H. Conrad Meyer, Foote Mineral Company, Philadelphia, Pennsylvania. (Ind. Eng. Chem. **30**, 431 (1938).)

The Carbonyls of the Less Familiar Elements. Arthur A. Blanchard, Massachusetts Institute of Technology, Cambridge, Massachusetts. (Cf. "Volatile Metal Carbonyls," Chem. Rev. **21**, 3 (1937).)

The Hydrous Oxides of Some Rarer Metals. H. B. Weiser and W. O. Milligan, Rice Institute, Houston, Texas. (J. Phys. Chem. **42**, 673 (1938).)

Newer Developments in Beryllium. C. B. Sawyer and B. R. Kjellgren, The Brush Beryllium Company, Cleveland, Ohio. (Ind. Eng. Chem. **30**, 501 (1938).)

Metallurgy of Tungsten and Molybdenum. Zay Jeffries and W. P. Sykes, General Electric Company, Cleveland, Ohio. (To be published in the *Journal of Chemical Education.*)

Recent Developments in Tantalum and Columbium. Clarence W. Balke, Fansteel Metallurgical Corporation, North Chicago, Illinois. (Ind. Eng. Chem. **30**, 251 (1938).)

The Platinum Group Metals. Fred E. Carter, Baker and Company, Inc., Newark, New Jersey.

Indium. Occurrence, Recovery and Uses. R. E. Lawrence and L. R. Westbrook, Grasselli Chemicals Department, E. I. du Pont de Nemours and Company, Cleveland, Ohio. (Ind. Eng. Chem. **30**, 611 (1938).)

Optical Lithium Fluoride. H. C. Kremers, The Harshaw Chemical Company, Cleveland, Ohio. (Probably to be published in *Industrial and Engineering Chemistry.*)

Organometallic Compounds of Indium. Walter C. Schumb and H. Irving Crane, Massachusetts Institute of Technology, Cambridge, Massachusetts. (J. Am. Chem. Soc. **60**, 306 (1938).)

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Gallium. Laurence S. Foster, Brown University, Providence, Rhode Island. (Probably to be published in the *Journal of Chemical Education.*)

Magnetic Measurements in Rare Earth Chemistry. P. W. Selwood, Northwestern University, Evanston, Illinois. (Probably to be published in the *Journal of the American Chemical Society.*)

The Use of the Arc Spectra for the Quantitative Determination of the Members of the Rare Earth Group. C. N. McCarty, L. R. Scribner, and Margaret Lawrenz with B. S. Hopkins, University of Illinois, Urbana, Illinois. (Ind. Eng. Chem., Anal. Ed. **10**, 184 (1938).)

The Chemistry of Germanium and its Compounds. Warren C. Johnson, University of Chicago, Chicago, Illinois.

The Analytical Chemistry of Columbium and Tantalum. Thomas R. Cunningham, Union Carbide and Carbon Research Laboratories, Inc., Niagara Falls, New York. (Ind. Eng. Chem., Anal. Ed. **10**, 233 (1938).)

Distribution of Rhenium. Clarence Hiskey and Loren C. Hurd, University of Wisconsin, Madison, Wisconsin. (To be published in *Industrial and Engineering Chemistry, Analytical Edition.*)

Behavior of Rhenium in Analysis. G. E. F. Lundell and H. B. Knowles, National Bureau of Standards, Washington, D. C.

Osmium Tetroxide. Don M. Yost and LeRoy H. Anderson, California Institute of Technology, Pasadena, California. (To be published in the *Journal of the American Chemical Society* as "The Properties of Osmium Tetroxide in Carbon Tetrachloride Solution. The Thermodynamic Constants of Osmium Tetroxide.")

Use of Less Familiar Elements in Vitreous Enamel Frits. Glenn H. McIntyre, Ferro Enamel Corporation, Cleveland, Ohio. (To be published by the Technical Staff of the Ferro Enamel Corporation, 4150 East 56th Street, Cleveland, Ohio.)

Use of Less Familiar Elements in Ceramic Pigments. Carl J. Harbert, The Harshaw Chemical Company, Cleveland, Ohio. (Published as "Less Familiar Elements in Ceramic Pigments," Ind. Eng. Chem. **30**, 770 (1938).)

THE CONCENTRATION OF THE LESS FAMILIAR ELEMENTS THROUGH IGNEOUS AND RELATED ACTIVITY[1]

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Received July 6, 1938

Throughout the ages mankind has been striving to increase the usefulness of the tools which he uses for providing himself with sustenance, with greater creature comforts, and with weapons of offense and defense. The archaeologist designates the great historical periods as the stone age, the bronze age, and the iron age, and implies thereby an increase in man's ability to use available materials in the making of his artifacts. We are now living in an age which can no longer be designated with the name of any single material. It is true that the present may still be called the iron age; nevertheless aluminum has become a potent factor in gradually lessening the dominance of iron. Aluminum is even more abundant in the earth's crust than iron and has the desirable property of lightness. Its utilization was delayed until a method was found for obtaining it in a high degree of purity from its ores. This has been accomplished only within the last forty years.

The present age, with its emphasis on speed, demands that the materials used in the construction of its artifacts shall be produced at low cost and shall possess lightness and resistance to deformation and corrosion. In the effort to secure these properties, the chemist is encouraged to study more intensively the chemical and physical properties of elements which are less common in the earth's crust than iron and aluminum. One outstanding result of this effort is the addition of magnesium to the list of commonly used metals. It is useful by itself but is even more useful when alloyed with aluminum.

Table 1 shows that the three elements iron, aluminum, and magnesium are among the most abundant elements. We have learned to use, either by themselves or as alloys, a host of metallic elements that are present in the earth in minor or even very low concentrations. Many of them, on the basis of our chemical and physical knowledge of their properties, are

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[1] This paper was presented at the Second Annual Symposium of the Division of Physical and Inorganic Chemistry of the American Chemical Society, held at Cleveland, Ohio, December 27–29, 1937.

TABLE 1

Average composition of igneous rocks

Major and common elements*

ELEMENTS	1	2	3	4
Oxygen	46.59	46.41	47.29	47.2
Silicon	27.72	27.58	28.02	28.0
Aluminum	8.13	8.08	7.96	8.0
Iron	5.01	5.08	4.56	4.5
Calcium	3.63	3.61	3.47	3.5
Sodium	2.85	2.83	2.50	2.5
Potassium	2.60	2.58	2.47	2.5
Magnesium	2.09	2.09	2.29	2.5
Titanium	0.63	0.720	0.46	0.33
Phosphorus	0.13	0.157	0.13	0.22
Hydrogen	0.13	0.129	0.16	0.17
Manganese	0.10	0.124	0.078	0.075
Sulphur	0.052	0.080	0.10	0.06
Barium	0.050	0.081	0.093	0.03
Chlorine	0.048	0.096	0.063	0.04–0.025
Chromium	0.037	0.068	0.034	0.01
Carbon	0.032	0.051	0.13	0.22
Fluorine	0.030	0.030	0.10	0.04–0.025
Zirconium	0.026	0.052	0.017	0.02–0.01
Nickel	0.020	0.031	0.020	0.005
Strontium	0.019	0.034	0.034	0.005
Vanadium	0.017	0.041	0.017	0.00n
Cerium, yttrium	0.015	0.020		0.00nn
Copper	0.010	0.010		0.000,n
Uranium	0.008	0.000,00n		0.000,00n
Tungsten	0.005	0.000,00n		0.000,00n
Lithium	0.004	0.005	0.004	0.004
Zinc	0.004	0.004		0.000,n
Columbium, tantalum	0.003	0.000,00n		0.000,000,n
Hafnium	0.003			
Thorium	0.002	0.000,00n		0.000,000,n
Lead	0.002	0.002		0.000,n
Cobalt	0.001	0.003		0.00n
Boron	0.001	0.001		0.00n
Glucinum	0.001	0.001		0.00n
	100.000	100.000	100.000	100.000

* The data are taken from Clarke and Washington (5) and show the averages obtained by several workers in this field. The reader is referred to the sources cited in the reference for further details. The numbers at the head of the columns refer to authors cited in reference 5.

rated as common elements. Surely copper, silver, gold, the platinum metals, lead, zinc, mercury, bismuth, manganese, titanium, nickel, and chromium are familiar elements, yet as compared with iron, aluminum; and magnesium they are, with respect to the earth's crust, uncommon. They are used either alone or in alloys; the alloys of nickel and chromium with iron have enormously increased the usefulness of this common element. It can be truly said that we are living in an age of alloys.

We are not concerned with the metals only, for many of the elements are most useful to man when they are combined with the two most abundant elements, namely, silicon and oxygen; the enormous development of the ceramic industries is a case in point.

This age is also becoming increasingly more dependent on substances that exercise a controlling influence on both chemical and physical processes. Catalysis and electron emission have assumed an importance that is out of all proportion to the amount of material used. In the constant endeavor to find materials that will increase catalytic action and electron emission and that will increase the usefulness of our commonly employed elements, it is quite natural that more attention will be given not only to the common and abundant ones but also to the rare and less familiar ones.

In this paper an element will be considered as rare when its concentration in the earth's crust (38) falls below 0.01 per cent, as shown in tables 1 and 2. When we consider the mass of the lithosphere (19×10^{18} metric tons) (5), the total amount of any of these is enormous, but this capacity factor is of little use if the cost of extraction is not commensurate with the market value of the product. It is true that gold, one of the rarest of elements, can be extracted economically from rather lean materials, but if all countries were to abandon the gold standard there would be but little gold extracted. Radium, in spite of its great value and usefulness, would remain a fascinating chemical curiosity but for the fact that it has been concentrated in uranium ores which in themselves represent a concentration from leaner material. The elements beryllium, molybdenum, vanadium, tungsten, thorium, the "rare earths," tantalum, and surely radium are very rare elements, but our chemical and physical knowledge of their properties has increased to such an extent that they are less familiar only to those who do not have occasion to work with them; they are now extensively employed in the industries. It is quite possible that cesium, rubidium, columbium, thallium, gallium, and even rhenium will soon be in the same category of useful elements.

None of the rare elements is likely to be useful unless we find it concentrated in nature to such an extent that it can be economically extracted with respect to market conditions. It is opportune, therefore, to review our knowledge, scanty though it may be, of the probable methods of concentration by natural processes.

Igneous rocks constitute 95 per cent of the crust of the earth (5). They are the source of the shales, sandstones, limestones, and soil that make up the remaining 5 per cent. It is obvious, therefore, that they must also be the source of all known elements. The geochemistry of the various elements considers their distribution throughout the earth. Since we have factual knowledge of only 3 per cent of its radius (28), our information concerning the more deeply seated portions must be by analogy with the meteorites or by inference from the data derived from seismological studies (2).

While it is true that the discussion of the distribution of the rare elements deep within the earth and in meteorites does not come within the scope of this discussion, a brief review of the findings of Ida and Walter Noddack (29) will be worth while. They have made analyses of the rare elements in meteorites, in extremely scarce rocks of deep-seated origin, in igneous rocks, and in sedimentary rocks. Their analyses indicate the same low concentrations recorded in tables 1 and 2. It is not at all unlikely, therefore, that most of the concentrations remain low throughout the stages of differentiation indicated below on account of the scarcity of the elements. Every analyst will appreciate the difficulty of removing a slight trace of some impurity which persists no matter how many operations he may use to remove it through concentration, either as a precipitate or by solution. It has been said that the best analysis is only an asymptotic approach to perfection (40). The research worker in seeking for the rare elements must therefore resort to the keenest of analytical tools such as optical and x-ray spectroscopy and must often combine them with chemical methods that permit coprecipitation of the rare with more readily removed elements. Given sufficient material and sensitive methods of analysis it is quite probable that all elements can be determined in any rock, but it is far more important to know how they have been concentrated in nature (23).

Geologists are now in fair agreement that such igneous rocks as are now amenable to investigation have in a great measure been derived from a homogeneous igneous mass by a process of differentiation. The theory of petrographical provinces (21) indicates that this homogeneous mass may have had a uniform bulk composition; nevertheless it gave birth to rock sequences that differed with respect to mineral species in different parts of the original mass. It is well to bear in mind, however, that while it is true that differentiation has taken place in many localities, there are huge igneous masses called batholiths that have been intruded under the crust of the earth and have crystallized and cooled without differentiation (24). Much remains to be done to give us a clearer view of these processes, but even though our knowledge concerning the nature of the materials

TABLE 2

Average composition of igneous rocks

Less common and rare elements*

ELEMENTS	5	6	7
Cerium, yttrium	1.5×10^{-4}	2×10^{-4}	$n \times 10^{-5}$
Copper	1×10^{-4}	1×10^{-4}	$n \times 10^{-6}$
Uranium	8×10^{-5}	$n \times 10^{-8}$	$n \times 10^{-8}$
Tungsten	5×10^{-5}	$n \times 10^{-8}$	$n \times 10^{-8}$
Lithium	4×10^{-5}	4×10^{-5}	4×10^{-5}
Zinc	4×10^{-5}	4×10^{-5}	$n \times 10^{-6}$
Columbium, tantalum	3×10^{-5}	$n \times 10^{-8}$	$n \times 10^{-9}$
Hafnium	3×10^{-5}		
Thorium	2×10^{-5}	$n \times 10^{-8}$	$n \times 10^{-9}$
Lead	2×10^{-5}	2×10^{-5}	$n \times 10^{-6}$
Cobalt	1×10^{-5}	3×10^{-5}	$n \times 10^{-5}$
Boron	1×10^{-5}	1×10^{-5}	$n \times 10^{-5}$
Glucinum	1×10^{-5}	1×10^{-5}	$n \times 10^{-5}$
Molybdenum	$n \times 10^{-6}$	$n \times 10^{-6}$	$n \times 10^{-7}$
Rubidium	$n \times 10^{-6}$	$n \times 10^{-6}$	$n \times 10^{-5}$
Arsenic	$n \times 10^{-6}$	$n \times 10^{-6}$	$n \times 10^{-5}$
Tin	$n \times 10^{-6}$	$n \times 10^{-6}$	$n \times 10^{-5}$
Bromine	$n \times 10^{-6}$	$n \times 10^{-6}$	$n \times 10^{-5}$
Cesium	$n \times 10^{-7}$	$n \times 10^{-7}$	$n \times 10^{-8}$
Scandium	$n \times 10^{-7}$	$n \times 10^{-7}$	$n \times 10^{-12}$
Antimony	$n \times 10^{-7}$	$n \times 10^{-7}$	$n \times 10^{-5}$
Cadmium	$n \times 10^{-7}$	$n \times 10^{-7}$	$n \times 10^{-8}$
Mercury	$n \times 10^{-7}$	$n \times 10^{-7}$	$n \times 10^{-8}$
Iodine	$n \times 10^{-7}$	$n \times 10^{-7}$	$n \times 10^{-5}$
Bismuth	$n \times 10^{-8}$	$n \times 10^{-8}$	$n \times 10^{-9}$
Silver	$n \times 10^{-8}$	$n \times 10^{-8}$	$n \times 10^{-9}$
Selenium	$n \times 10^{-8}$	$n \times 10^{-8}$	$n \times 10^{-9}$
Platinum	$n \times 10^{-9}$	$n \times 10^{-9}$	$n \times 10^{-10}$
Tellurium	$n \times 10^{-9}$	$n \times 10^{-9}$	$n \times 10^{-10}$
Gold	$n \times 10^{-9}$	$n \times 10^{-9}$	$n \times 10^{-10}$
Iridium	$n \times 10^{-10}$		
Osmium	$n \times 10^{-10}$		
Indium	$n \times 10^{-11}$	$n \times 10^{-11}$	$n \times 10^{-11}$
Gallium	$n \times 10^{-11}$	$n \times 10^{-11}$	$n \times 10^{-11}$
Thallium	$n \times 10^{-10}$	$n \times 10^{-10}$	$n \times 10^{-11}$
Rhodium	$n \times 10^{-11}$		
Palladium	$n \times 10^{-11}$		
Ruthenium	$n \times 10^{-11}$		
Germanium	$n \times 10^{-11}$	$n \times 10^{-13}$	$n \times 10^{-12}$
Radium	$n \times 10^{-12}$	$n \times 10^{-14}$	

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* The data are taken from Clarke and Washington (5). The numbers at the head of the columns refer to authors cited in reference 5. The authors obviously consider these values as orders of magnitude. It is quite possible that these figures will have to be changed when more accurate data are obtained, but it is doubtful if the changes will significantly alter these orders of magnitude.

below the earth's crust is limited, considerations based on the study of seismic phenomena, elasticity of rocks (1), and phase rule studies (4, 28) of the rocks that have been brought to the surface have produced theories which, in spite of the fact that they must later be either amplified or discarded altogether, are helpful in giving us a picture of what is probably going on.

On the basis of the known density of the earth taken as a whole, about 5.5, and the density, 2.8, of the known granitic shell which makes up the bulk of the earth's crust, it naturally follows that the earth's core must contain material of higher density. On the basis of analogy with the composition of meteorites it is assumed that the core is composed of the two metals nickel and iron. The study of seismic phenomena, the known compressibility of rocks and their elastic properties, and the analyses of igneous rocks all indicate that there are three principal shells covering the core. The bulk composition of the layer next to the core corresponds to that of a peridotite, the next shell to that of a basalt, and the surface layer to that of a granite. The statistical studies of Clarke and Washington (5) confirm this theory with respect to the surface shell, for they show that in spite of the many different kinds of igneous rocks, the bulk composition corresponds to that of a granite. It is possible that the basaltic shell with its relatively low silica content grades into the siliceous granite.

Geologists believe that rocks of low silica content such as eclogites and peridotites are of deep-seated origin; the physicist has found from his studies that the known rocks that would account for the observed sudden increase in velocity of seismic waves are just these eclogites and peridotites.

The granitic shell is believed to be about 60 kilometers thick and somewhat unevenly distributed. It is thickest in the continental masses and thins out to almost nothing in the great oceanic deeps. The average analysis of the rocks of the earth's crust certainly points to a granitic composition, but the intrusion into the shell and extrusion on the surface by igneous activity of rocks of different composition varying from a basalt to a rhyolite show clearly that a process of differentiation has taken place. The depth (6) at which these changes took place is at present a matter of conjecture, but it quite probably happened below the granitic shell. Our knowledge concerning the distribution of the rare or less familiar elements has been derived, of course, from the layer whose average composition is a granite. Yet the very fact that differentiation has taken place is a matter of considerable interest, for in this manner minerals of economic importance have been concentrated (36).

Poulett Scrope (32) was one of the earliest investigators to promulgate the idea that a huge mass of heated igneous material under the surface of the earth could differentiate. "It is quite conceivable that, when exposed in the focus of a volcano to successive liquefaction and reconsolidation, the heavier minerals may sink by a sort of filtration through the lighter ones, the upper portions of the mass becoming consequently more felspathic, the lower more ferruginous or augitic." This beautifully simple theory was bitterly opposed by many geologists, but the entire problem was once more taken up by Schweig (31) in the light of the advances made in geology and physical chemistry. Relatively little attention was paid even now to this newer presentation of differentiation. About ten years later, the work of Bowen (4) truly aroused the interest of the geologists in this problem. By this time, however, the experimental side of petrography received such decided support from phase rule considerations and from the new experimental technique developed at the Geophysical Laboratory of the Carnegie Institution, that Bowen could with much greater assurance point out to the geologist that fractional crystallization in a large body of molten magma can take place. Objections (10) have been raised to parts of Bowen's theory; nevertheless the definite possibility and probability of such differentiation have been demonstrated.

In this brief résumé of differentiation mention has been made only of siliceous rocks. It is well at this point to call attention to the work of Vogt (35) and Goldschmidt (11), who consider it possible that some basic magmas have become so greatly enriched in sulfur that sulfides of the heavy metals, particularly sulfides of iron and nickel, may have separated on cooling. Goldschmidt (11) postulates that an original fluid globe separated on cooling into three immiscible layers: at the core a metallic melt, which grades into one in which the sulfides dominate, and this in turn grades into a siliceous shell containing a gas phase,—the atmosphere. It is believed by some geologists that the well-known platinum-rich copper nickel sulfide ore bodies of Sudbury have resulted from a process of differentiation through fractional crystallization, but there is as yet no unanimity of opinion on this point. The sulfide ores are, however, associated with a huge mass of intruded igneous rocks, and it is believed that magmatic differentiation played an important rôle in their origin. This also seems to apply to the segregation of the platinum metals in many basic rocks of the Ural Mountains in Russia, Columbia, California, and South Africa, and to the segregation of chromite, magnetite, and the titanium-iron mineral ilmenite (24), but even here the influence of post-magmatic effects of aqueous solutions and volatile constituents is not denied.

Considerable impetus has recently been given to the elucidation of the theory of segregation and concentration of the sulfides by Merwin and Lombard (25). This is the first attempt to apply phase rule principles to these vaguely understood processes. The three-component system, copper, iron, and sulfur, was studied at various temperatures and at a definite vapor pressure of sulfur. The region of stability of the iron sulfides, the copper sulfides, the copper–iron sulfides, and of a series of solid solutions of the various sulfides was thereupon determined.

As differentiation progresses in the more acidic portions of the large igneous masses that have been considered in this review, the volatile constituents, such as water, hydrogen chloride, hydrogen fluoride, hydrogen sulfide, and carbon dioxide, that were present in solution begin to assert themselves by virtue of their becoming more concentrated. It is now well established that water to the extent of about 1 or 2 per cent can lower the fusion point of difficultly fusible rocks such as a granite by over 300°C. Morey (26) and Goranson (19) have shown that as crystallization and cooling in a closed system continue, the volatile constituents, especially water, can generate enormous pressures on the constraining mantle. If the mantle is not strong enough to withstand the pressure it will be ruptured, and igneous materials, including the gases, will be injected through volcanic activity. It is also possible that the constraining mantle may be strong enough to withstand rupturing, but the boiler pressure, so to speak, is great enough to permit the injection of the siliceous mass of material into weaker layers of the mantle. It is by some such mechanism as this, together with probable chemical activity on the surrounding rock, that it is believed the end products of differentiation, namely, the pegmatite dikes (24), are formed. These masses of material injected under high gas pressure are the happy hunting ground for those in search of rare elements (14). Many of these elements have reached such a high degree of concentration that when combined with other elements they crystallize as distinct mineral species. The boron-bearing minerals, the rare earths, the cesium mineral pollucite, the lithium- and cesium-rubidium-bearing micas, the fluoborates, the fluorides, and the beryllium minerals are examples. They also contain many minerals such as molybdenite, within which have been concentrated some of the extremely rare elements of which rhenium is an example. We have now reached a stage in the differentiation in which volatile constituents, especially water, play an important rôle. It was said above that there are relatively few sulfide deposits whose origin by magmatic segregation is unambiguous. The reason is that near the end of the various processes of differentiation water and other volatile constituents, such as carbon dioxide, hydrogen chloride, hydrogen fluoride, boron, and hydrogen sulfide, at temperatures which we know from field and laboratory evidence may be as high as 650°C., accumulate and produce an intensely chemically active environment. Very little of a fundamental nature is known of this complicated system. At present it can not be studied as an entirety and must be broken down into a simpler form. This has been done for part of the system iron–chlorine–water by Stirnemann (33). Similar fundamental studies of vapor phase activity are now being carried out by Morey and his coworkers (27). The problem, by virtue of the intense chemical activity of its components, is extremely difficult, but at least an attempt must be made to obtain its solution if we wish to coördinate field evidence with laboratory investigation.

The term "water" was applied to one of the constituents in the igneous materials, but it is perhaps best to give it its usual designation of H_2O, for in the environment mentioned above it is above its critical temperature and the properites of liquid and vapor become indistinguishable. As cooling takes place it will exist in both phases, and all the active chemicals referred to may be either in solution or in the vapor phase. Naturally the intensity of the chemical activity will depend on temperature and percentage concentration. This point will be discussed again later in this review. It must be obvious from what has been said that the record of any magmatic segregation of constituents that may have taken place can be destroyed in its entirety by virtue of the chemically active gases that are produced in the last stages of differentiation. It is not amiss to call attention to the fact that "geological field research deals with end phenomena of completed reactions but with a very imperfect record of the earlier steps in the earth-making process" (7).

On page 54 the condition was postulated that the pressure of the vapor phase generated on crystallization of the silicate magma may reach such proportions that rupturing of the constraining mantle may take place. We thus have in its simplest form the beginning of volcanic activity which is, therefore, the surface manifestation of more deep-seated activity. We no longer have a completely closed system, and all the changes brought about by virtue of change in pressure and lowering of temperature will take place. The phenomena are not necessarily confined to the surface, for the hearth of the volcano may still be several miles below the orifice; nevertheless the physical-chemical environment is that of an essentially open system in which chemical changes may take place quite rapidly.

We have reached a stage in the history of an igneous body which is more or less amenable to direct study. Volcanic phenomena have been observed for a long period of time and naturally more attention has been given to the description of types of solid materials, the dust clouds, the lava, and the fragmental material which contribute to the construction of the volcanic edifice. Some of the earlier writers on volcanic activity realized that the extrusion of solid materials certainly accounts for the bulk of the material brought to the surface, but they also recognized the fact that at many volcanoes vapors, especially water, played a very important part in providing the mechanism by which the solid materials were brought to the surface (28, 32). In the course of the early part of this century attention was directed specifically to these vapors and to the minerals which were formed by the interaction of the vapors with the constituents in the extruded rocks. The story is not quite so simple as just stated. The rock materials that are brought to the surface are not necessarily composed of the minerals and constituents in the last stages of differentiation. Interaction with the constraining mantle may take place in the hearth of the volcano and introduce material which may have quite a different composition. Then, too, interaction of the chemical vapors with this material may bring about a sequence of changes quite different from those peculiar to the unaltered segregation. The possibility, however, exists of coordinating field studies in nature's laboratory at volcanoes with fundamental studies carried out under carefully controlled conditions.

The volcanic eruption that took place in 1912 in the Valley of Ten Thousand Smokes (3, 9, 39) located on the Alaskan Peninsula offered an unusual opportunity for studying the chemical aspects of the later stages of igneous activity. The activity in the Valley was, according to Fenner (9), brought about by the injection of the very siliceous lava, rhyolite, under the old floor of the Valley. The pressure exerted by the volatile constituents was sufficient to rupture the floor and permit the igneous materials to reach the surface. The lava was highly charged with volatiles which on sudden relief of pressure escaped into the atmosphere and deposited a great mass of hot and very porous glassy pumice. The Valley is roughly four miles wide and twelve miles long, and it is estimated that a cubic mile of material was extruded. Thousands of fumaroles (steam vents) were situated in this rhyolitic pumice, and in 1919, seven years after the eruption, were quite active both thermally and chemically. Steam temperatures as high as 640°C. were found, indicating that the temperature of the more deeply buried material was still quite high. Allen and Zies (3) collected and analyzed the fumarole gases and found that they contained about 99.5 per cent of water, 0.2 per cent of gases insoluble in water, and a total of 0.3 per cent of the acid gases hydrogen chloride, hydrogen fluoride, and hydrogen sulfide. The bulk of the gas is obviously steam, but we must not be misled by the low concentration of the other gases. An estimate (39) was made of the total amount of gases that would be emitted if the rate observed in 1919 were to continue. This is only an estimate, to be sure, but reasons have been given in the references cited for believing that it is of the right order of magnitude. It is seen from table 3 that even though the percentage concentration of the dominant acid constituents is small, yet the total amount from this single volcanic area is enormous. It is essential, therefore, in dealing with these natural phenomena to keep both the intensity and the capacity factors clearly in mind.

The presence of large total amounts of fluorine is particularly noteworthy, for it is one of the most active of the acid gases in decomposing silicates. The interaction of the acid gases with the extruded pumice decomposed the latter and set free a host of halides, sulfides, and oxides whose presence in the pumice was not even surmised. The reader is referred to the original articles (39) for the detailed account of the investigations. It will suffice for our present purpose to call attention to a few items of geochemical importance. Our interest was first directed to the concentration of minor elements when we found barium in the incrustations around the vents in amounts that represented a hundredfold increase over that determined in the pumice itself. Magnetite (Fe_3O_4) was found in many of the vents, and, although no reliable estimate could be made of the total amount, it was obvious that it must be thought of in terms of tons rather than a few pounds. The evidence is also clear that the magnetite was derived through a vapor phase activity and represents, therefore, the concentration of the iron derived from the more deeply seated portions of the pumiceous deposit. The magnetite was so beautifully crystallized that one might easily assume that we were dealing with a relatively pure material. The analysis in table 4 shows, however, that this was far from the truth.

TABLE 3

Amount of acid gases emitted in 1919 by the fumaroles in the Valley of Ten Thousand Smokes (39)

Estimated volume of steam calculated at 100°C. and 760 mm. = 26 × 10^6 liters per second

GAS	PER CENT	GAS CONTAINED IN STEAM	METRIC TONS OF GAS PER YEAR
		kg. per second	
HCl	0.117	36.0	1.3 × 10^6
HF	0.032	5.6	0.2 × 10^6
H_2S	0.029	8.4	0.3 × 10^6

When it was found that a well-crystallized mineral such as magnetite could contain so many extraneous minor elements, it was decided to subject the other incrustations that had been collected to detailed chemical and spectrographic analysis. It was then discovered that many elements were present other than those found in the magnetite. Thus bismuth, gallium, thallium, boron, germanium, arsenic, selenium, and tellurium were definitely proved to be present. Molybdenum was found not only in the magnetite but in the other incrustations as well, often in the form of the hydrated oxide molybdenum blue. The concentration of this compound was great enough to color areas covering half an acre.

The pumiceous material in its purest form was next subjected to the same analytical procedure, and every element found in the incrustations was shown to be present in the pumice. The concentration in the incrustations was almost one hundred times that in the pumice. Practically all the elements mentioned above have one characteristic in common: namely, their halides, and, in some cases, their sulfides and oxides are volatile at the temperatures prevailing in the Valley of Ten Thousand Smokes. We obviously have here a mechanism by which large amounts of elements present in traces in the igneous materials can be concentrated at or near the surface and brought up from more deeply buried materials. The condition is here met that in order to bring about this type of concentration there must be a constant shifting of equilibrium due to lowering of the pressure and temperature. Niggli (28) has given considerable thought to the volatile products of igneous materials and has clearly presented the theories underlying the probable changes that take place on the cooling

TABLE 4

Foreign constituents in the fumarolic magnetite found in the Valley of Ten Thousand Smokes (39)

WEIGHT OF SAMPLE	WEIGHT OF SUBSTANCE AS DETERMINED	CALCULATED AS	PER CENT
grams	*grams*		
10		Hg	None
10	0.0007 PbO	Pb	0.005
10		Bi	None
10	0.0233 Cu	Cu	0.23
10	0.0054 MoO_3	Mo	0.04
10	0.0005 SnO_2	Sn	0.004 (approximate)
10		As	None
10		Sb	Present*
10		Cr	None
10		V	None
10	Colorimetrically	TiO_2	0.005
10	0.0474 Zn	Zn	0.47
10	0.0005 $NiC_8H_{14}N_4O_4$	Ni	0.01
10	0.0003 CoO	Co	0.02
1	Colorimetrically	MnO	0.13
1	0.0196 $BaSO_4$	S	0.27
20	0.0110 NaCl + KCl	NaCl	0.05
10	0.0530 siliceous residue		0.53
1	0.0005 Al_2O_3†		

* Definitely identified spectroscopically and not present in the blank.

† Present in the portion of fumarolic magnetite soluble in hydrochloric acid, and indicates that alumina was not present as part of the magnetite molecule.

of a magma. It will repay those interested in this phenomenon to study his presentation carefully.

In a sense this period of expulsion of volatile constituents is the last stage of what may be called true igneous activity, but it is by no means the last chapter in the study of concentration of the elements. One illustration will suffice. In 1923 Fenner continued his studies in the Valley of Ten Thousand Smokes and at our request made an effort to collect more of the magnetite found in 1919, but none was found. The temperatures had fallen to a point where active condensation of the steam was taking place; the acid gases were now in solution, and the magnetite was decomposed. The influence of hydrogen sulfide was now apparent, for in the new chemical environment only such compounds could persist as are relatively insoluble in acid. In place of magnetite, such minerals as covellite (CuS), chalcocite (Cu_2S), and sphalerite (ZnS) were found. These represent a further concentration of the copper and zinc. This illustration is cited to show the complex mechanism by which concentration is brought about.

These are in brief the methods by which concentration of the elements may be attained in nature. We have seen, however, that many of the rare and less familiar elements are present in igneous materials in such extremely low concentrations that it is possible for them to be dragged along as persistent impurities, so to speak, throughout the process of rock differentiation. It would seem almost futile to hope to find them in the rocks in any concentration of economic importance, no matter how valuable their chemical or physical properties may be. The case is not so hopeless, however, as it may seem.

In the discussion of the formation of the pegmatite dikes it was stated that some of the rare elements may be too dilute to form a definite mineral yet may be trapped by other minerals. Every analyst is familiar with a related process. For instance, extremely minute amounts of fluorine can be carried out of a neutral solution if barium is added and subsequently precipitated as barium sulfate. Gallium often escapes detection when present in low concentrations, but it can be concentrated by hydrogen sulfide if zinc is present. This phenomenon of coprecipitation is but little understood, but in the writer's opinion it is an important agency in concentrating some of the rare elements. There is still another mechanism by which minerals can gather up elements that exist in solution at low concentration. The magnetite found in the Valley of Ten Thousand Smokes contained appreciable amounts of manganese and zinc within the magnetite itself. This reminds one of the important mineral group called the spinels, of which magnetite and the zinc- and manganese-bearing franklinite are examples. Still another example: the cesium, rubidium, and gallium often found in lepidolite, one of the many minerals found in pegmatite dikes, can be fairly easily concentrated in the alums that are readily obtained after the mica is decomposed.

Grimm (20) has shown that the ability to form such mixed crystals depends on the dimensions of similarly constructed crystals and also on the dimensions of the substituted atom species. Goldschmidt (11 to 18), a most indefatigable worker on the problem of the distribution of the elements, has in a series of articles called attention to the high degree of probability that the segregation of the elements in crystals is governed by the relation between crystal structure and the dimensions of the atom and ion species. If this is true, then in the course of the crystallization of the various mineral species all extraneous elements whose atomic or ionic dimensions are either too small or too large to be taken up by the crystals are concentrated in the mother liquor. Perhaps the finest contribution made by Goldschmidt (12) is his determination of the ionic radii of many of the elements in Angström units. The values of the radii are based on x-ray studies of crystal structure, which furnish the so-called lattice dimensions, and on the determinations by Wasastjerna (22) of the ionic dimensions of F^- and O^{--}. The assumption is also made that in general the anion–cation distances of closest approach should be given by the sum of the corresponding radii (22). X-ray studies of a large number of combinations of the elements with oxygen, fluorine, and sulfur were made by Goldschmidt in order to obtain a basis for his calculations. Pauling also calculated the ionic distances from different data and obtained results that agree well with those of Goldschmidt. These results are tabulated in the International Tables for the Determination of Crystal Structure (22). They apply to distinct crystal groups, and due regard must be given to the structure type, valency, and coördination number. The interested reader is referred to the citations for the necessary details. These ionic and atomic dimensions provide us with a powerful tool for following the

TABLE 5

*Lattice dimensions of similar compounds of aluminum and gallium**

ALUMINUM COMPOUNDS	LATTICE DIMENSIONS	LATTICE DIMENSIONS	GALLIUM COMPOUNDS
	Å.	Å.	
Al_2O_3	5.13	5.28	Ga_2O_3
$LaAlO_3$	3.78	3.89	$LaGaO_3$
AP	5.451	5.436	GaP
AlAs	5.628	5.635	GaAs
AlSb	6.091	6.093	GaSb

* Taken from Goldschmidt (13).

probable course of the segregation of the elements that exist in minor concentration in the rocks, and have enabled Goldschmidt (17) to make several trenchant observations. The lattice dimensions of similar aluminum and gallium compounds are shown in table 5. This striking similarity in dimensions is also reflected in the similarity of the ionic radii.

In table 6 are shown the ionic radii of a few elements of equal valency. They are arranged in groups of similar dimensions, and a common element is associated with an element whose average concentration in the earth's crust is low. They have been selected for this presentation because this same association is repeatedly found in nature.

TABLE 6

*Similarity in ionic radii of rare elements of equal valency camouflaged by the common elements**

ELEMENT	IONIC RADIUS	ELEMENT	IONIC RADIUS	ELEMENT	IONIC RADIUS	ELEMENT	IONIC RADIUS	ELEMENT	IONIC RADIUS
	Å.		Å.		Å.		Å.		Å.
Mg........	0.78	Si........	1.27	Al.......	0.57	Si........	0.39	Zr.......	0.87
Ni........	0.78	Pb.......	1.32	Ga.......	0.63	Ge.......	0.44	Hf.......	0.86

* Taken from Goldschmidt (13).

TABLE 7

*Similarity in ionic radii of the yttrium elements**

ELEMENT	IONIC RADIUS	ELEMENT	IONIC RADIUS	ELEMENT	IONIC RADIUS
	Å.		Å.		Å.
Gd................	1.11			Ho................	1.05
Tb................	1.09	Y................	1.06	Er................	1.04
Dy................	1.07			Yb................	1.00
				Cp................	0.99

* Taken from Goldschmidt (13).

The same striking similarity in ionic radii obtains for the trivalent yttrium series of elements (see table 7). The analyst finds it extremely troublesome to separate these elements, and nature has had the same difficulty. The average percentage concentration of these elements in the earth's crust is extremely low; they are not removed by the usual processes of differentiation and therefore are concentrated in the mother liquor,—the pegmatites. Many other examples could be cited, but for our purpose the above will suffice.

Goldschmidt (17) has given the name "Tarnung" or "camouflage" to this tendency for the rare elements to be associated with and obscured by some more common element whose concentration in the siliceous igneous fluids is high enough to form a distinct mineral. He has also shown that extraneous elements whose valencies differ but whose ionic radii are similar may also be concealed or camouflaged within some common mineral. Table 8 contains several examples for both the common and the rare elements.

Many years ago Washington (37) called attention to the fact that calcium is frequently found with sodium in the soda feldspars, and barium with the potassium feldspars. Goldschmidt's work, based on x-ray studies of crystal structure and x-ray analysis, now provides an explanation for the association of the elements referred to and has thereby given great impetus to the study of their geochemistry.

The geochemical cycle of germanium as worked out by Goldschmidt and Peters (15) is of unusual interest. The former, on the basis of similarity in dimensions of ionic radii, had indicated that this element should be associated with silicon in the silicates. Papish (30) by means of his spectrographic analyses showed that germanium is in fact widely distributed in silicate minerals. Goldschmidt and Peters (16) showed that germanium could probably be absorbed by the roots of plants. They found for instance 1.6 per cent of GeO_2 in the ashes derived from some English coals, surely an extraordinary concentration of what is usually called a rare element.

TABLE 8

*Similarity in ionic radii of elements differing in valency camouflaged by the common elements**

ELEMENT	IONIC RADIUS	VALENCY	ELEMENT	IONIC RADIUS	VALENCY
	Å.			Å.	
Li	0.78	1	Ca	1.06	2
Mg	0.78	2	Y	1.06	3
Na	0.98	1	Sc	0.83	3
Ca	1.06	2	Zr	0.87	4
K	1.33	1	Ti	0.64	4
Ba	1.43	2	Nb	0.69	5

* Taken from Goldschmidt (13).

The geochemistry of rhenium has been studied very thoroughly by its discoverers, Ida and Walter Noddack (29). A truly enormous number of substances have been analyzed by them within a comparatively short time both by x-ray and by optical spectroscopy. No claim seems to be made by them for great accuracy of the determinations; nevertheless their work brings out clearly where this extremely rare element is likely to be found in nature. Here, again, similarity in ionic radii seems to be the guiding principle in showing that the greatest concentrations will be found in the molybdenites associated with pegmatitic minerals. Molybdenum and rhenium are much alike in their chemical properties and in the dimensions of their ionic radii. The work of Ida and Walter Noddack also brings out a point that has been frequently referred to, namely, the investigation of the by-products and so-called waste materials in the industries. Rhenium has been extracted from a molybdenum by-product in amounts that definitely take this element out of the category of a chemical curiosity (8).

Even though the useful elements found in ore bodies were derived from igneous materials through the processes of differentiation referred to in this review, yet their present concentration has in most cases been obtained through a complicated process of decomposition of the original materials and their reconcentration from solution in a favorable physical-chemical environment. The rare elements camouflaged in some mineral may also be reconcentrated when this mineral is decomposed through subsequent geochemical alteration.

It would behoove those who are interested in searching for the rare elements that are not found as distinct mineral species to sharpen their quantitative physical and chemical analytical tools and search for these less familiar elements in the minerals and waste products within which the guiding principle of similarity in ionic radii has shown they may be concealed. It will also be desirable to take cognizance of the chemical principles referred to in the discussion of the concentration of the elements in volcanic areas through vapor phase activity and through the solvent action of acid or even alkaline waters.

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THE COÖRDINATING TENDENCY OF THE METALLIC IONS[1]

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The postulate of coördinate valence, conceived by Alfred Werner in 1893 and stated in terms of the electron theory by Sidgwick thirty years later, has now become one of the foundation stones of chemical thought. Originally devised to explain the existence of metal ammines and similar compounds, it is now used in every field of chemistry, and coördinate valence is recognized as one of the fundamental modes of atomic and ionic union. Yet there are many questions concerning coördination which the coördination theory does not explain. It is the purpose of this paper to call attention to a few of those questions, especially some involving coördinated metallic ions.

These "complex" ions are much more common than is usually realized. Many compounds ordinarily regarded as "simple" are in reality complex, as physical-chemical investigations amply show. For example, electrolysis of scandium sulfate solution shows that even in dilute solution part of the scandium is in the anion, so that the formula for the salt should evidently be written $Sc[Sc(SO_4)_3]$ (26). The parallel case of cadmium iodide is well known. Coördinated metal compounds vary in stability from those which are not decomposed at red heat (for example, some of the acetylacetonates) to those which exist only in the presence of excess of their components. The latter group is typified by the "double salts," which give analytical tests for the simple ions and at the same time give indications of complex ion formation. The interesting work of McBain and Van Rysselberghe (17) should be mentioned in this connection. These investigators reported that in the electrolysis of mixtures of salts, one of the metal ions frequently migrates to the anode, and must therefore be part of an anionic complex. For example, in a solution 0.95 molar in potassium sulfate and 0.05 molar in magnesium sulfate, the magnesium migrates toward the anode. In other cases the migration of the ion toward the cathode is greatly hindered, but not reversed. Their interpretation has been criticized by Freed and Kasper (10) and by Houlton and Tartar (12). Freed and Kasper measured the magnetic susceptibilities of solutions of potassium sulfate and manganous sulfate and of mixtures of the two. On the assumption that complex formation would be accompanied by a decrease in magnetic susceptibility (an assumption which later work has been shown to be questionable (19)), they concluded that no complex ion was formed in the mixture, although transference experiments showed that the migration of the manganous ion toward the cathode was greatly surpressed. They attribute this effect to a clustering of sulfate ions around the manganous ion. Houlton and Tartar (12) studied the Raman spectra of solutions of potassium and manganous sulfates and mixtures of them, and found that the mixtures gave no Raman lines which were not given by the pure salts, from which they concluded that no complexes are formed between the two. In interpreting experiments like those of Freed and Kasper and of Houlton and Tartar it should be kept in mind that solutions of manganous salts do not contain the simple manganous ion, but a hydrated manganous ion, or possibly the $Mn(SO_4)_2^{--}$ ion, so that the manganese–oxygen coördinate bond is present before the other sulfate is added.

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[1] Adapted from a paper presented at the Second Annual Symposium of the Division of Physical and Inorganic Chemistry of the American Chemical Society, held at Cleveland, Ohio, December 27–29, 1937.

Werner supposed that each element and ion has a definite coördination number—that is, that it can surround itself with a definite number of coördinating groups. Werner's coördination numbers range from two to twelve, with six as the most common. While this assumption clears up many difficulties, it leaves many others completely unexplained. Compounds such as $ThCl_4 \cdot 20NH_3$ (29) and $Na_2CO_3 \cdot 10H_2O$ do not fit into the scheme at all. Werner made various assumptions to bring these exceptions into line with his theory—he assumed "double molecules" occupying one coördination position and molecules of solvent being held mechanically to a salt without definite chemical union—but in many cases even these assumptions failed to make the theory fit the facts. Some interesting work along this line has been done by Peters (20), who has shown from a large number of examples that when dry salts take up ammonia, the number of ammonia molecules held is frequently six or a multiple of six. In the latter case he assumes that both the cation and anion combine with ammonia. Spectral comparison of $CuCl_2 \cdot 6NH_3$ and $CuPtCl_6 \cdot 18NH_3$ indicates to him that only six molecules of ammonia are attached to the copper ion in the latter compound. The chloroplatinate ion must then hold twelve molecules. The spectral studies may be open to criticism because they were carried out in rather dilute aqueous solution, in which part of the ammonia might well have dissociated from the molecule. However, the solid salts are nearly the same color, the slight difference probably being due to the color of the chloroplatinate ion. If we accept Peters' conclusion, we must agree that the coördination number of platinum becomes eighteen, or that the twelve ammonia molecules are attached to the chloride ions (thus expanding the chloride octet to ten or twelve), or that they are held in place by some force as yet unexplained. Peters' results, however, might also be explained by assuming that the cupric ion can coördinate triple as well as single ammonia molecules without sensibly changing the color of the complex, which is due to the linkage of the copper with the nitrogen.

Pfeiffer and Tappermann (25) have carried out similar studies, using the tridipyridyl and tri-ortho-phenanthroline complex ions of nickel, iron, cobalt, zinc and cadmium. Salts of these ions crystallize with large amounts of water, at least part of which (usually six molecules) is attached to the positive ion, although the normal coördination number of the metal is satisfied by the three molecules of the organic amine.

Brintzinger and Osswald (2), by a study of dialysis coefficients, have shown that hydration effects of this sort frequently occur in solution. Thus, the triethylenediamine cobaltic ion seems to exist in solution as $[\mathrm{Co\,en_3(H_2O)_{12}}]^{+3}$. Surprisingly, the closely related hexammine cobaltic ion $[\mathrm{Co(NH_3)_6}]^{+3}$ is not hydrated.

Using the same technique, Brintzinger and Ratanarat (3) found that many of the "simple" ions are highly hydrated in solution. Among the cations are $[\mathrm{Al(H_2O)_{18}}]^{+3}$, $[\mathrm{Fe(H_2O)_{18}}]^{+3}$, $[\mathrm{Cr(H_2O)_{15}}]^{+3}$, $[\mathrm{Th(H_2O)_{12}}]^{+4}$, and $[\mathrm{Be(H_2O)_{12}}]^{+2}$, while some of the commoner anions are $[\mathrm{SO_4(H_2O)_2}]^{-2}$, $[\mathrm{C_2O_4(H_2O)_4}]^{-3}$, $[\mathrm{PO_4(H_2O)_{24}}]^{-3}$, and $[\mathrm{AsO_4(H_2O)_{24}}]^{-3}$.

By means of dialysis experiments Brintzinger and his colleagues (4) have determined ionic weights of many complex ions, and have shown that they not infrequently are capable of forming super-complex ions. Thus, they write $\{[\mathrm{Cr\,pn_3}](\mathrm{SO_4})_4\}^{-5}$, $\{[\mathrm{Co_2pn_6}](\mathrm{HAsO_4})_4\}^{-2}$, and many others. (The symbol "pn" represents propylenediamine.)

It seems quite evident that atoms and ions can have coördination numbers much greater than Werner suggested, or that several concentric coördination shells can be held around a single atom. Such concentric shells can be formed whenever the coördinating group can act both as donor and acceptor. In the hydrates and ammines this is accomplished through hydrogen bonds. The interesting compound $\mathrm{A \cdot 16BF_3}$ discovered by Booth and Willson (1a) is probably formed in an analogous way.

That real chemical union exists between such "extra" molecules and the complex ion has been demonstrated by the stereochemical experiments of Pfeiffer and Quehl (24). They showed, for example, that the rotatory power of zinc α-bromo-π-camphorsulfonate is almost doubled by the addition of ortho-phenanthroline, which unites with the zinc to form a complex ion, $[Zn(phen)_3]^{+2}$, in which the zinc is apparently coördinately saturated. Pfeiffer and Quehl say that asymmetry is "induced" in this ion by the presence of the optically active bromocamphorsulfonate ion in the solution. It does not seem possible that this can happen without some sort of union between the two ions. Several other examples of this effect have been reported (23).

Many factors must be taken into account in considering the stability of coördination compounds. The effect of temperature is obvious, and is illustrated by the decomposition of hydrates upon heating. Pressure is an important factor if the coördinating groups are volatile. The nature of the "central ion" of the complex is of extreme importance. In general, the tendency to form coördination compounds is shown most strongly by the transition elements, but is by no means limited to them. Attempts to predict coördinating tendency and coördination number on the basis of the periodic table are not entirely successful, as irregularities frequently appear. Thus the hydroxides of chromium, cobalt, and nickel dissolve in excess ammonium hydroxide, forming ammines, but those of manganese and iron do not. Platinous and palladous ions usually show a coördination number of four, but the nickelous ion, in spite of its smaller size, has a coördination number of six.

The interesting theory of Sidgwick (27) should be mentioned in this connection. It postulates that each ion tends to take up electrons from coordinating groups until it achieves the structure of the next noble gas. Thus the cobaltic ion, having twenty-four electrons, gains an additional twelve by coördinating six groups, and assumes the stable structure of krypton. However, there are several exceptions to the theory, and the tendency to build to a rare gas structure is overshadowed by other considerations. This has been discussed in detail by Mann (16).

The valence of a metal ion frequently influences its coördination tendency. Thus, $PtCl_2$ combines with four molecules of ammonia, but $PtCl_4$ combines with six. Palladous and palladic ions show the same variation. Hantzsch and Rosenblatt (11) have denied that the coördination number varies, suggesting instead that the platinous compound is a "pseudo-salt," $[PtCl_2 \cdot (NH_3)_4]$. In solution water molecules displace the chloride ions from the complex, giving $[Pt(H_2O)_2(NH_3)_4]^{+2}$ and $2Cl^-$. Upon crystallization the reverse reaction takes place. While the theory is supported by a considerable amount of evidence, it has not been tested enough to win widespread acceptance.

The coördinating power of a cation is greatly influenced by the anion with which it is united. This may be illustrated by the compounds of barium, of which the chloride and bromide form stable hydrates with two molecules of water, the iodide with six, and the hydroxide with eight.

The relative sizes of the ions are altered by hydration until a close-packed crystal lattice can be formed.

The nature of the anion may also influence the union of neutral molecules with metallic ions in another way. The anion may lose its ionic nature, in whole or in part, by coördinating with the cation, this occupying part of its coördination sphere and altering its properties. Thus, triethylenediamine chromic chloride is stable above 200°C., but the corresponding thiocyanate loses one molecule of ethylenediamine at 160°C., forming $[\mathrm{Cr\,en_2(SCN)_2}]\mathrm{SCN}$ (22). Effects of this sort sometimes make it difficult to determine the true coördination number of a metallic ion.

The nature of the coördinating ("donor") group is one of the most important factors in determining the stability of coördination compounds. It is not possible, however, to arrange the various donor groups in a series in the order of their coördinating power, for this changes as the coördinated metal ion is changed. The cyanide ion forms very stable complexes with ferrous and ferric ions, and much less stable ones with nickel ion. On the other hand, ammonia coördinates much more readily with nickel than with ferrous or ferric ions. No satisfactory explanation of this has been advanced.

The nature of the donor group may even determine the coördination number of an ion, as Mann (16) has shown. Zinc, platinous, and palladous ions normally coördinate only four amine groups, but form very stable hexammine complexes with α,β,γ-triaminopropane, utilizing all six of the amine groups from two triaminopropane molecules.

Almost any neutral or negative group which has a pair of unshared electrons may act as a donor group. The most important neutral groups are ammonia, organic amines, water, alcohols, and organic sulfides. However, hydrogen sulfide, phosphine, aliphatic phosphines and arsines, ketones, unsaturated hydrocarbons, and many other compounds can act as donor groups. Even phosphorus trichloride is known to form coördination compounds (7). Of the negative groups, cyanide, thiocyanate, hydroxide, and the halide ions are most frequently encountered, but almost any negative ion can function as a donor group.

If the donor group forms a chelate ring with the metal ion, the strength of the union is much enhanced. Ethylamine coördinates weakly, but ethylenediamine forms very stable compounds. Complex compounds of pyridine are much less stable than those of dipyridyl. This effect is shown, however, only if the chelate ring contains five or six members. Decamethylenediamine has very little tendency to coördinate. A complete discussion of the chelate rings may be found in the recent paper of Diehl (8).

The coördinating ability of acetylacetone deserves special mention. Not only does acetylacetone coördinate with a very large number of positive ions, including its own enolic hydrogen ion, but some of its compounds are characterized by an unparalleled degree of stability. This may be due to resonance of the carbon–carbon double bond in the chelate ring.

Tables 1 to 7 have been compiled to indicate the coördinating power of some of the more common donor groups. Those elements whose symbols are set in bold-face type form definite linkages with the group in question, while those elements whose symbols are set in italics form unstable or questionable compounds. Elements not so designated may form such linkages, but the literature seems to contain no mention of them. Water, the simpler alcohols, ammonia, and the halide ions coördinate with practically all of the metals, so tables were not prepared for them. Naturally, these coördination compounds vary greatly in stability, but quantitative measurements of stability have been made in very few cases. The ammines of some of the Group VIII metals are remarkably stable; thus, hexammine cobaltic chloride can be recrystallized from concentrated hydrochloric acid or warmed with sodium hydroxide solution without decomposition.

Among the halide ions the fluoride ion is the most interesting, because the metals usually show their highest coördination number when in union with fluorine.

The complex cyanides (table 1) present a compact group when arranged according to the Bohr periodic table. The metals in the center form the most stable cyanides, the stability decreasing rather uniformly as we proceed in either direction. Molybdenum and tungsten show a coördination number of eight toward the cyanide ion; for vanadium, chromium, and the metals of Groups VII and VIII this drops to six, and for the elements of the copper and zinc groups it is only four. It is hardly safe to generalize, but many examples could be cited to indicate that the coördination number of these transition elements tends to decrease as we proceed toward the right. This agrees qualitatively with Sidgwick's theory. There are so many exceptions, however, that it can hardly be taken as support of the theory.

Most of the metallic ions form compounds with the aliphatic amines (table 2). The simpler primary amines coördinate as firmly as ammonia itself (21), the stability of the union decreasing as the length of the carbon chain increases. Diamines coördinate more firmly than monoamines if they form suitable chelate rings. Secondary amines have less tendency to coördinate than primary amines; in tertiary amines (except heterocyclics) the tendency is almost lost. It appears very strongly with pyridine, ortho-phenanthroline, and similar bases (table 3).

The nitrite ion forms many very stable complexes (table 4). In most of these we have a nitrogen–metal bond rather than an oxygen–metal

TABLE 1

Cyanides

1	H																		He
2	Li	Be											Be	B	N	O	F		Ne
3	Na	Mg											Al	Si	P	S	Cl		A
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br		Kr
5	Rb	Sr	Yt	Zr	Cb	Mo	Ma	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I		X
6	Cs	Ba	RE*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po			Nt
7		Ra	Ac	Th	U^x	U													

*RE = rare earths.

TABLE 2

Aliphatic amines

1	H																		He
2	Li	Be											B	C	N	O	F		Ne
3	Na	Mg											Al	*Si*	P	S	Cl		A
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br		Kr
5	Rb	Sr	Yt	Zr	Cb	Mo	Ma	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I		X
6	Cs	Ba	RE	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po			Nt
7		Ra	Ac	Th	U^x	U													

TABLE 3

Pyridine, phenanthroline, etc.

1	H																	He
2	Li	Be											B	C	N	O	F	Ne
3	Na	Mg											Al	Si	P	S	Cl	A
4	K	*Ca*	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	Rb	Sr	Yt	Zr	Cb	Mo	Ma	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	X
6	Cs	Ba	RE	Hf	Ta	*W*	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	*Bi*	Po		Nt
7		Ra	Ac	Th	U^x	U												

TABLE 4

Nitrites (nitro)

1	H																	He
2	Li	Be											B	C	N	O	F	Ne
3	Na	Mg											Al	Si	P	S	Cl	A
4	K	*Ca*	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	*Zn*	Ga	Ge	As	Se	Br	Kr
5	Rb	*Sr*	Yt	Zr	Cb	Mo	Ma	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	X
6	Cs	*Ba*	RE	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	*Bi*	*Po*		Nt
7		Ra	Ac	Th	U^x	U												

TABLE 5

Unsaturated hydrocarbons

1	H																	He
2	Li	Be											B	C	N	O	F	Ne
3	Na	Mg											Al	Si	P	S	Cl	A
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	*Ni*	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	Rb	Sr	Yt	Zr	Cb	Mo	Ma	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	X
6	Cs	Ba	RE	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po		Nt
7		Ra	Ac	Th	U^x	U												

TABLE 6

Amino acids

1	*H*																	He
2	*Li*	Be											B	C	N	O	F	Ne
3	*Na*	*Mg*											Al	Si	P	S	Cl	A
4	*K*	*Ca*	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	*Rb*	*Sr*	Yt	Zr	Cb	Mo	Ma	Ru	Rh	Pd	Ag	*Cd*	In	Sn	*Sb*	Te	I	X
6	Cs	*Ba*	*RE*	Hf	Ta	W	Re	Os	Ir	Pt	*Au*	Hg	Tl	Pb	Bi	Po		Nt
7		Ra	Ac	Th	U^x	U												

TABLE 7

d-Tartaric acid

1	H																	He
2	Li	Be											B	C	N	O	F	Ne
3	Na	Mg											Al	Si	P	S	Cl	A
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	Rb	Sr	Yt	Zr	Cb	Mo	Ma	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	X
6	Cs	Ba	RE	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po		Nt
7		Ra	Ac	Th	U^x	U												

bond, and the group is properly referred to as a "nitro" group. This has been proven by Chernyaev, who has reported that platinous nitro compounds can be reduced to platinous ammines by zinc and either hydrochloric or acetic acid (5). The metal–nitrogen bond must be present before reduction takes place, as ammonia will not coördinate with the metal ion in an acid solution.

Jorgensen prepared "nitrito" cobaltic complexes (13), containing an oxygen–cobalt bond. These are not stable, however, and rearrange to the isomeric nitro compounds.

The coördination of unsaturated hydrocarbons with metal ions (table 5) is of great theoretical interest, because electrons have to be withdrawn from the double bond before coördination is possible. (See, for example, the work of Anderson (1) and of Kharasch and Ashford (14).) This, however, leaves one of the carbon atoms with only a sextet. It is possible in some cases that this carbon atom is coördinated to the metal, in which case the metal is the "donor," rather than the "acceptor." Most of the theoretical work has been done on the platinum–olefin complexes, but many of the others are equally stable. Anhydrous aluminum and iron chlorides catalyze the Friedel–Crafts reaction through the formation of compounds of this type. Gallium chloride also catalyzes this reaction (28) and probably in the same way. No compounds have been isolated, however. The mercury–olefin compounds are of interest as intermediates in organic syntheses.

Other unsaturated organic groups may also coördinate with metal ions. The azo dyes unite with the mordant through the nitrogen–nitrogen double bond (9).

The amino acids (table 6) may coördinate with metal ions through the —NH_2 groups, or through the amino and carboxyl groups simultaneously. In the latter case, α-amino acids give extremely stable chelate rings. Cobalt alanine, for example, can be recrystallized from hot 50 per cent sulfuric acid (15). The interesting stereochemical possibilities offered by these compounds have been studied to some extent in the cases of cobalt and chromium. They offer a fertile field for research.

The hydroxy acids also form chelate rings. Tartaric acid (table 7) has found several applications as a coördinating agent. Its use in Fehling's solution is well known. It has recently been shown (18) that beryllium can be separated from aluminum, iron, copper, and chromium by precipitating it from a tartrate solution with ammonium hydroxide. The other metals do not precipitate. Still a third application is that of deBoer and Emmens (6), who have developed an interesting polarimetric method of determining the relative amounts of zirconium and hafnium in a mixture through the formation of optically active complex ions with dextrotartaric acid.

Tables might be prepared for many other donor groups, but the ones given suffice to bring out most of the periodic regularities and to indicate points at which research can profitably be undertaken.

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THE SYNTHETIC RADIOACTIVE ISOTOPES OF THE LESS FAMILIAR ELEMENTS[1, 2]

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The phenomenon of radioactivity was first observed by Becquerel in 1896 while he was working with compounds of uranium (4). Subsequent research by many investigators revealed more than forty atomic species having the property of spontaneously disintegrating by emitting charged particles. In 1919 Rutherford showed that it was possible to disintegrate stable nuclei by bombarding them with energetic alpha particles from natural radioactive sources (31). However, it was not until 1934 that radioactive isotopes were synthesized. At that time, Curie and Joliot observed exponentially decaying positron activities in boron, magnesium, and aluminum when these elements were bombarded with alpha particles (13). Since then, about two hundred radioactive isotopes of eighty-five of the chemical elements have been reported (26). The synthesis of radioactive elements by bombardment with alpha particles immediately suggested the use of other projectiles in effecting this type of synthesis. Deuterons, protons, neutrons, and gamma rays have all proved effective in bringing about the nuclear transformations necessary for the production of radioactive isotopes of the stable elements. These types of reaction will be briefly outlined.

METHODS OF PRODUCTION OF ACTIVE ISOTOPES

1. Alpha particles

Natural radioactive disintegrations furnish alphas of energies up to 8.8 M.e.v. which are very useful in producing radioactivity in the light elements (20). These are effective on elements up to calcium, whose atomic number is 20. Low intensity and limited energy are the most serious

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[2] Contribution No. 66 from the Research Laboratory of Inorganic Chemistry of the Massachusetts Institute of Technology.

drawbacks for this type of projectile. Recent work with $_2He^4$ ions accelerated in the cyclotron indicates that the use of alphas can be extended indefinitely. Radioactive isotopes of elements of atomic number up to 53 have already been produced by this means (22, 23, 34).

The capture of alpha particles with the simultaneous emission of protons or neutrons results in nuclei which are radioactive. In the first case the resulting nuclei exhibit both electron and positron activities, but in the second case only positron activities are observed.

2. Protons

Hydrogen ions, accelerated by any of the several methods available, can be used in producing nuclear reactions that lead to radioactive isotopes of the stable elements (11). This type of projectile has been most effective for light elements, but the use of more energetic protons from the cyclotron has already led to reactions involving elements of high atomic number (8).

Proton capture also follows two types of reactions. The first is accompanied by the emission of neutrons and yields nuclei that are electron- or positron-active. The second type does not involve a simultaneous particle emission but involves the emission of gamma rays, leaving nuclei that are positron-active.

3. Deuterons

More effective than protons or alphas for producing radioactive isotopes of the stable elements are deuterons. Because they have a smaller charge, penetration into the nucleus is easier than for alphas. At high energies they can split at the nucleus, allowing their neutron component to enter the nucleus while the proton component is repelled by the nuclear field (28). The energy necessary to effect nuclear transformations can be given these particles by any of the methods used for accelerating ions.

Most deuteron reactions are accompanied by simultaneous emission of alphas, protons, or neutrons. In the first two classes the residual nuclei can be electron- or positron-active; in the third class the nuclei are only positron-active.

4. Neutrons

Most effective of all particles for producing radioactive nuclei of the stable elements are neutrons (19). Fermi first used them for this purpose and showed that they induce activities in nearly all elements. Their great effectiveness lies in the fact that these particles have no nuclear charge, hence there is no Coulomb force opposing their entry into the nuclei of atoms. The neutrons used must be produced by some nuclear reaction, several of which are suitable. Alphas from radium and its decay products give fast neutrons from beryllium and less energetic neutrons from boron (9, 13, 17). The reaction of deuterons on deuterium furnishes a source of monoenergetic fast neutrons (5). A very intense source of neutrons is obtained by the action of deuterons on beryllium (12).

Neutron reactions fall into four classes: alphas, protons, gamma rays, or two neutrons may be products of the initial disintegration. The residual nuclei may then decay with the emission of electrons in the first three cases and either electrons or positrons in the fourth.

5. Gamma rays

Disintegration by gamma rays was first observed by Chadwick and Goldhaber, using gamma rays from ThC″ with ${}_1H^2$ (10). These natural gamma rays will also disintegrate ${}_4Be^9$, but are not effective on elements of higher atomic number (33). However, gamma rays of 17 M.e.v. are produced in the reaction between protons and lithium, and these very energetic gammas have been used by Bothe and Gentner for inducing radioactivity in elements of atomic number up to 73 (7). The reaction involves absorption of a photon and the emission of a neutron, and leaves nuclei which are either electron- or positron-active. This method of producing radioactive elements is important, for it allows the identification of the active isotope in many cases.

IDENTIFICATION OF ACTIVE ISOTOPES

In nuclear reactions the atomic number Z and the mass number A of bombarding particles are known, Z of the target is known, and A and Z for the lighter disintegration product can be determined. From this data the Z for the residual nucleus can be calculated. If the residual nucleus is radioactive, the value of Z can be checked by chemical separation of the active element and tracing its course with some counting device.

An excellent example of this procedure is found in boron, one of the first elements to be rendered radioactive. Boron bombarded with alphas gives neutrons (6). The resulting material has a single positron activity of 11 min. half-life. The reaction can thus be indicated:

$${}_5B^A + {}_2He^4 \rightarrow {}_0n^1 + {}^*_7X^{A+3} = {}^*_7N$$

A target of boron nitride after bombardment with alphas can then be treated with a sodium hydroxide solution which will form ammonia. This gas can be removed from the solution. It is then found that all of the positron activity is in the ammonia and none in the sodium orthoborate solution. In order to show conclusively that the nuclear reaction does not involve nitrogen, targets containing boron but no nitrogen and targets containing nitrogen but no boron can be used. The 11 min. activity will be found in the first target, but only the 70 sec. activity of $\overset{*}{_9}F^{17}$ in the second. This definitely establishes the atomic number of the target and of the residual nucleus.

There is now a final factor to be determined for this reaction, namely, the mass number of the target and product. A table of isotopes will show two isotopes of boron, with masses of 10 and 11. Considering first the most abundant isotope of mass 11, the equation for the nuclear reaction becomes:

$$_5B^{11} + {_2He^4} \rightarrow {_0n^1} + {_7N^{14}}$$

But $_7N^{14}$ is a stable isotope and would not emit positrons. If $_5B^{10}$ is taken, the residual nucleus is $_7N^{13}$.

This isotope has not been observed among the stable isotopes of nitrogen and is, therefore, considered the radioactive isotope formed in the reaction. The complete equation is then:

$$_5B^{10} + {_2He^4} \rightarrow {_0n^1} + \overset{*}{_7}N^{13} \rightarrow e^+ + {_6C^{13}}$$

The final product, $_6C^{13}$, is a stable isotope.

As a means of correlating the nuclear reactions observed and predicting other reactions, Evans and Livingston devised an isotope chart on which all of the stable isotopes found in nature have been plotted (18). In this chart the atomic numbers, Z, are plotted as abscissae and the "isotope numbers," $A - 2Z$, are plotted as ordinates. This isotope number represents the number of neutrons in the nucleus in excess of the number of protons.

The advantages of using this scale to represent the mass numbers are that the region of stable isotopes is clearly defined, the ordinates give directly the number of excess neutrons necessary for stable nuclei, and the vertical scale is shortened to a convenient length. If a nuclear reaction results in a product nucleus which lies above the region of stable isotopes, the nucleus will come back into that region by emitting an electron. If the resulting nucleus is below the region of stable isotopes, it will become stable by emitting a positron.

As an aid in clarifying nuclear reactions, the isotope chart may be used as follows: Bombardment of manganese and chromium with fast neutrons and vanadium with slow neutrons in each case yields an element which emits electrons (3). The decay period is 3.75 min. for all these targets, hence the product must be the same in all three reactions. In order to determine what is the product and how it is formed, the distribution of the isotopes of these elements must be studied (figure 1). The stable isotopes are $_{23}V^{51}$, $_{24}Cr^{50, 52, 53, 54}$, and $_{25}Mn^{55}$. The only reactions that will account for the results are:

$${}_{25}Mn^{55} + {}_0n^1 \rightarrow {}_2He^4 + {}^{*}_{23}V^{52}$$

$${}_{24}Cr^{52} + {}_0n^1 \rightarrow {}_1H^1 + {}^{*}_{23}V^{52} \qquad {}^{*}_{23}V^{52} \rightarrow e^- + {}_{24}Cr^{52}$$

$${}_{23}V^{51} + {}_0n^1 \rightarrow {}^{*}_{23}V^{52}$$

Chemical tests also indicate that the radioactive element is vanadium.

A similar group of reactions is found with manganese, iron, and cobalt as targets for neutrons.

RADIOACTIVE ISOTOPES AND THE PERIODIC TABLE

The periodic table has four places where the elements have not yet been isolated and identified beyond question. The missing elements are those of atomic numbers 43, 61, 85, and 87.

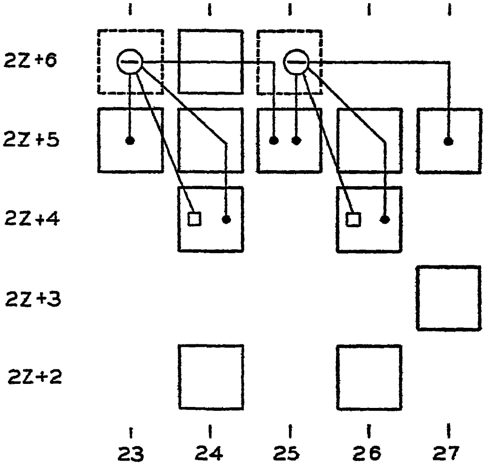

FIG. 1. Distribution of the isotopes of elements of atomic number 23 to 27

It is probable that element 61, illinium, is naturally radioactive. This would account for the difficulty in obtaining it in an appreciable quantity. Samarium is definitely radioactive, emitting alpha particles (15). This activity can be assigned to ${}_{62}Sm^{152}$ on the basis of studies of the hyperfine structure (32). Beta activity has been detected in neodymium (24). Maurice Curie has reported a beta activity in the middle fractions of a neodymium–samarium mixture which would be most likely to contain element 61 (16). The complete chain of reactions can be represented as:

$${}_{62}Sm^{152} \rightarrow {}_2He^4 + {}_{60}Nd^{148} \rightarrow e^- + {}_{61}Il^{148} \rightarrow e^- + {}_{62}Sm^{148}$$

The discoveries of the other three missing elements have been reported, but the claims have not been definitely established in any case (27, 2, 1).

In order to obtain some idea of their chemical properties, it would be desirable to obtain synthetic radioactive isotopes of these elements.

For element 43, masurium, these have been prepared by the following nuclear reactions (25, 29):

$${}_{44}\mathrm{Ru}^{A} + {}_{1}\mathrm{H}^{2} \rightarrow {}^{*}_{43}\mathrm{Ma}^{A-2} + {}_{2}\mathrm{He}^{4}$$

$${}_{42}\mathrm{Mo}^{A} + {}_{1}\mathrm{H}^{1} \rightarrow {}^{*}_{43}\mathrm{Ma}^{A} + {}_{0}n^{1}$$

$${}_{42}\mathrm{Mo}^{A} + {}_{1}\mathrm{H}^{2} \rightarrow {}^{*}_{43}\mathrm{Ma}^{A+1} + {}_{0}n^{1}$$

There are several other nuclear reactions that would be expected to yield a radiomasurium. These have not been successful to date.

The last of the three reactions above yields a radiomasurium of long half-life (several weeks). This activity has been used in the investigation of the chemical properties of element 43 (29).

Using a piece of molybdenum bombarded for several months by high energy deutrons from the Berkeley cyclotron, Perrier and Segrè have shown that the long-life electron activity is due to element 43. Chemical separations eliminated molybdenum, columbium, zirconium, and ruthenium, leaving only masurium as the possible carrier of the activity.

When manganese and rhenium are added to solutions containing the radiomasurium, the activity is found to follow rhenium much more closely than manganese. The characteristic reactions of rhenium were also characteristic of masurium with one exception. Concentrated sulfuric acid (80 per cent) containing rhenium and radiomasurium remained active when moist hydrogen chloride was passed through the solution. The rhenium was carried out by the gas stream. This was the only chemical reaction resulting in an appreciable separation of the two elements.

A study of the isotope chart indicates one possible reaction of all the types now known that would produce element 85 (figure 2). Bismuth has one stable isotope, ${}_{83}\mathrm{Bi}^{209}$. If this were bombarded with very energetic alphas, element 85 might be produced according to the reaction:

$${}_{83}\mathrm{Bi}^{209} + {}_{2}\mathrm{He}^{4} \rightarrow {}_{0}n^{1} + {}^{*}_{85}\mathrm{X}^{212} \rightarrow e^{+} + {}_{84}\mathrm{ThC}'^{212}$$

The resulting nucleus should be positron-active, since it lies below the region of naturally occurring isotopes. The testing of this reaction must wait until instruments for the production of extremely energetic alphas are available.

There are two possible reactions for the production of a synthetic radioelement 87 (figure 2). The probability of these ever being tried are very slight, however, since the practical difficulties involved are almost insurmountable. The only target material available for the reaction is radium.

Expense, danger of handling, and experimental difficulties due to natural decay products make this possibility one of theoretical interest only. The nuclear reactions mentioned are:

$$_{88}\mathrm{Ra}^{221} + {}_{0}n^{1} \rightarrow {}_{1}\mathrm{H}^{1} + {}_{87}\mathrm{X}^{226} \rightarrow e^{-} + {}_{88}\mathrm{Ra}^{226}$$
$$_{88}\mathrm{Ra}^{226} + {}_{1}\mathrm{H}^{2} \rightarrow {}_{2}\mathrm{He}^{4} + {}_{87}\mathrm{X}^{224} \rightarrow e^{-} + {}_{88}\mathrm{ThX}^{224}$$

Among the nuclear reactions of the less familiar elements that are of unusual interest are those involving bismuth, thorium, and uranium. The first of these elements, bismuth, gives with deuteron bombardment a radioactive product that is identical with RaE, a natural radio-isotope of bismuth (25). The reaction is (figure 2):

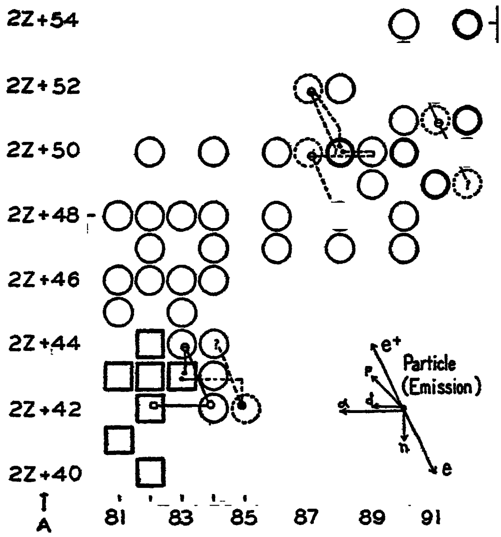

FIG. 2. Distribution of the isotopes of elements of atomic number 81 to 92. Solid circles represent natural radioactive isotopes. Heavily outlined isotopes are of elements which can be separated in weighable amounts.

$$_{83}\mathrm{Bi}^{209} + {}_{1}\mathrm{H}^{2} \rightarrow {}_{1}\mathrm{H}^{1} + {}_{83}\mathrm{RaE}^{210} \rightarrow e^{-} + {}_{84}\mathrm{RaF}^{210} \rightarrow {}_{2}\mathrm{He}^{4} + {}_{82}\mathrm{RaG}^{206}\ (\mathrm{Pb})$$

Thorium and uranium both lead to new radioactive series on bombardment with neutrons. In this way they differ from the lighter radioactive elements which give stable isotopes upon decay.

The synthetic radioactivity in thorium has been carefully studied by Curie, Halban, and Preiswerk (14). They have identified by chemical tests the four active products and have established a genetic relationship

TABLE 1

*A selected list of synthetic radioactive isotopes of the elements**

ATOMIC NO.	SYMBOL	ACTIVITY	HALF-LIFE	ATOMIC NO.	SYMBOL	ACTIVITY	HALF-LIFE
6	C	e^+	20.5 min.	48	Cd	e^-	4.3 hr.
7	N	e^+	11 min.	49	In	e^-	2.3 hr.
9	F	e^+	112 min.	50	Sn	e^-	28 hr.
11	Na	e^+ and e^-	6 months and	51	Sb	e^-	2.5 days
			14.8 hr.	52	Te	e^-	1 hr.
14	Si	e^-	170 min.	53	I	e^-	25 min.
15	P	e^-	14.5 days	55	Cs	e^-	1.5 hr.
16	S	e^-	80 days	56	Ba	e^-	85.6 min.
17	Cl	e^+	37 min.	57	La	e^-	31 hr.
18	A	e^-	110 min.	59	Pr	e^-	19 hr.
19	K	e^-	12.2 hr.	60	Nd	e^-	1 hr.
20	Ca	e^-	2.4 hr.	62	Sm	e^-	2 days
21	Sc	e^+	52 hr.	63	Eu	e^-	9.2 hr.
23	V	e^+	16 days	64	Gd	e^-	8 hr.
25	Mn	e^+	5 days	65	Tb	e^-	3.9 hr.
26	Fe	e^-	40 days	66	Dy	e^-	2.5 hr.
27	Co	e^-	1 year	67	Ho	e^-	35 hr.
28	Ni	e^+	3 hr.	68	Er	e^-	12 hr.
29	Cu	e^+ or e^-	12.8 hr.	69	Tm	e^-	8 months
30	Zn	e^-	100 hr.	70	Yb	e^-	3.5 hr.
31	Ga	e^-	23 hr.	71	Lu	e^-	6 days
32	Ge	e^-	30 min.	72	Hf	e^-	1 month
33	As	e^-	26 hr.	73	Ta	e^-	200 days
34	Se	e^-	56 min.	74	W	e^-	23 hr.
35	Br	e^-	36 hr.	75	Re	e^-	20 hr.
37	Rb	e^-	22 hr.	76	Os	e^-	40 hr.
38	Sr	e^+	3 hr.	77	Ir	e^-	3 days
39	Y	e^-	70 hr.	78	Pt	e^-	14.5 hr.
40	Zr	e^-	40 hr.	79	Au	e^-	2.7 days
42	Mo	e^-	36 hr.	80	Hg	e^-	40 hr.
43	Ma	e^-	46 days	81	Tl	e^-	1.3 hr.
44	Ru	e^-	11 hr.	82	Pb	e^-	8.6 days
45	Rh	e^-	1.1 hr.	83	Bi	e^-	5 days
46	Pd	e^-	12 hr.				
47	Ag	e^+	25.5 min.				

* This list is one selected from a complete list (26) of synthetic radioactive elements as of July 1, 1937. The purpose of the selection was to indicate those elements whose half-lives are of sufficient length to make them useful as chemical indicators.

between two of them (figure 2). On this basis they postulated another radioactive series of the type $4n + 1$. Their scheme is:

$$ {}_{92}U^{237} \rightarrow {}_{2}He^{4} + {}_{90}Th^{233} \xrightarrow[25\ \text{min}]{} e^- + {}_{91}Pa^{233} \xrightarrow[2.5\ \text{min.}]{} e^- + {}_{92}U^{233} \rightarrow {}_{2}He^{4} + {}_{90}Th^{229} \rightarrow {}_{2}He^{4} + {}_{88}Ra^{225} \rightarrow \text{etc.} $$

In order to see if such a series existed in nature they examined carefully purified uranium and concluded that if it did exist, its abundance was $<1/10{,}000$ of the $4n + 2$ series.

Neutron bombardment of uranium leads to a very complex group of activities which have been thoroughly investigated by Hahn, Meitner, *et al.* (21). Three distinct radioactive series result, all of which lead to elements of successively higher atomic number by electron emisson. This situation is without parallel, as all other series emit alpha particles after one or two beta emissions. Elements to atomic number 96 have been identified by chemical tests, and no evidence of alpha emission has been obtained. These interesting series of nuclear transformations should add much to our understanding of the upper limit of the periodic table (30).

The longer lived synthetic radioactive isotopes of the less familiar elements are given in table 1. Also listed are the radioactive isotopes of the more common elements that have long enough half-lives to make them useful as chemical indicators. Today it is usually possible to obtain from the larger hospitals, for experimental purposes, radon seeds which can be used in radon–beryllium neutron sources. With this source of activation and with the artificial sources available in several of the larger universities, more research should be directed into those fields opened up by the powerful new tool of chemistry, the synthetic radioactive isotopes of the stable elements.

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THE TRANSURANIUM ELEMENTS

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I. INTRODUCTION

Since the discovery of artificial radioactivity, a new significance has become attached to certain ideas which have persisted in the minds of scientists for a considerable period of time. What is the maximum possible number of elements? Do elements exist beyond uranium in the atomic series? If there are elements beyond uranium, what are their properties? The advent of artificial radioactivity revived research along these lines, which has resulted in the synthesizing of elements of atomic number greater than 92.

The chemical literature contains reports of the detection of transuranium elements based on chemical separations and physical measurements of materials obtained from minerals, none of which has been verified. Conjectures as to the total possible number of elements have been recorded from time to time. Predictions as to the properties of elements beyond uranium have been made by different investigators. Finally, because radioactivity may be induced in atoms, it has been possible to produce certain of the transuranium elements in very minute amounts and to determine some of their properties, but several very important points remain to be solved.

Uranium has been known for a long time, Klaproth having first reported its discovery in 1789. Over a century later, in 1895–96, came the discovery of radioactivity by Becquerel. Investigation of this new property of matter showed that it was exhibited by uranium as well as by several other atomic species. Ultimately the three major disintegration series were distinguished one from the other, and uranium was named as the parent substance of one series. The idea still persisted, however, that perhaps in earlier times there were other radioactive substances now nonexistent, or that perhaps elements exist whose radioactive properties are such that the methods of detection and measurement in use have not been sensitive enough to permit their discovery.

II. CLAIMS REPORTED FOR THE EXISTENCE OF ELEMENT 93 IN MINERALS

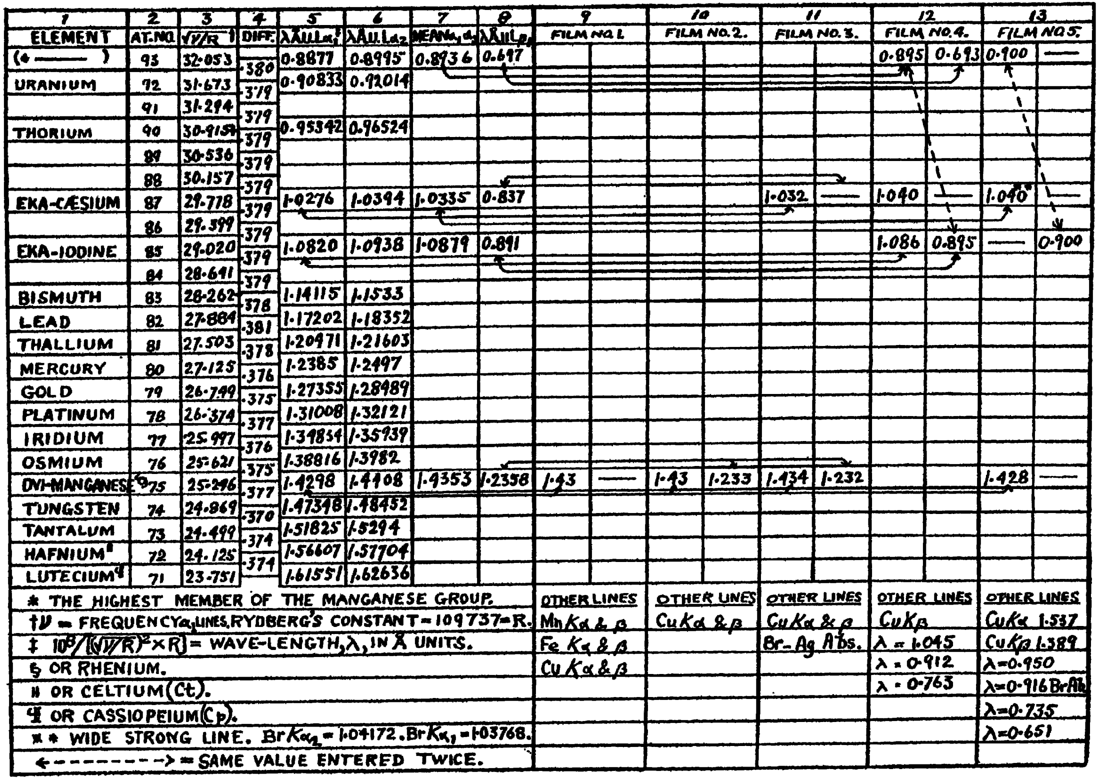
The possible existence of element 93, a transuranium element, has been twice reported since the advent of x-ray spectroscopy as a method of analysis. A series of articles by Druce and Loring (25, 56, 57, 58) appeared in 1925 and 1926, reporting their investigations on manganese materials. Primarily they were interested in detecting elements 43 and 75. Before making their spectroscopic analyses it was necessary for them to calculate the characteristic x-ray lines for several of the heavier elements. Using the values given by Siegbahn for the known elements, they determined the characteristic lines for elements 43, 75, 85, 87, 93 and for the radioelements of the different disintegration series. Table 1 gives a summary of these values. In their discussion foreshadowing element 93, they suggested that two very distinct lines observed on two x-ray films might possibly be the $L\alpha_1$ and the $L\beta_1$ lines of the highest member of the manganese group. The observed wave lengths of these lines were 0.895 and 0.693 Å. as compared with the estimated values of 0.8936 and 0.697 Å., respectively. No definite claim for the detection of element 93 was advanced.

In 1934 considerable interest was manifested in an announcement by Odolen Koblic (50, 51, 52, 53), director of the National Uranium and Radium Plant in Joachimsthal, Czechoslovakia, that an element possessing an atomic weight greater than that of uranium had been discovered in Joachimsthal pitchblende. The name "bohemium" and the atomic number 93 were assigned to the newly found element. It was said to have an atomic weight of 240, based on the analysis of its silver salt, $\mathrm{Ag}\mathit{93}\mathrm{O}_4$. Koblic had reasoned that uranium was not the last member of the atomic series but that an element 93 must exist as the parent substance of protoactinium and the actinium series. Such an element would thus be a congener of manganese and rhenium. Its most stable compounds would be analogous to the perrhenates. $\mathrm{H}\mathit{93}\mathrm{O}_4$ would thus be a very strong acid. Its sodium salt would be very soluble, whereas the analogous thallous salt would be difficultly soluble. These two facts would permit isolation of the element, if it occurred in a mineral. With this in mind, Koblic treated the material obtained in the decomposition of the pitchblende. The mineral is used normally for the production of uranium and radium preparations. The first stage in breaking it down consists of treatment with soda ash and leaching. Koblic reasoned that the mother liquor from this alkali treatment should contain the element 93, so he evaporated a large quantity of the liquor to a small volume. The crystalline deposit thus secured contained the excess soda ash, saltpeter, and other soluble salts. The clear filtrate was further concentrated to remove additional amounts of soluble salts. The clear mother liquor obtained from this treatment was acidified with nitric acid and then treated with an excess of silver nitrate. The precipitate obtained was removed by filtration, and the clear filtrate treated with thallous nitrate. A red, crystalline precipitate formed, which was the expected $\mathrm{Tl}\mathit{93}\mathrm{O}_4$. This salt was converted into the more soluble silver salt, of which 115 mg. was obtained. From the

TABLE 1

characteristic x-ray lines of elements 71 to 93, as calculated by F. ng

(Reprinted from Chem. News **131**, 339 (1925))



1	2	3	4	5	6	7	8	9		10		11		12		13	
ELEMENT	AT. NO.	$\sqrt{\nu/R}$ †	DIFF.	λÅU. $L\alpha_1$ ‡	λÅU. $L\alpha_2$	MEAN $\alpha_1\alpha_2$	λÅU. $L\beta_1$	FILM NO. 1.		FILM NO. 2.		FILM NO. 3.		FILM NO. 4.		FILM NO. 5.	
(* ———)	93	32·053		0·8877	0·8995	0·8936	0·697							0·895	0·693	0·900	—
URANIUM	92	31·673	·380	0·90833	0·92014												
	91	31·294	·379														
THORIUM	90	30·915	·379	0·95342	0·96524												
	89	30·536	·379														
	88	30·157	·379														
EKA-CÆSIUM	87	29·778	·379	1·0276	1·0394	1·0335	0·837					1·032	—	1·040	—	1·040**	—
	86	29·399	·379														
EKA-IODINE	85	29·020	·379	1·0820	1·0938	1·0879	0·891							1·086	0·895	—	0·900
	84	28·641	·379														
BISMUTH	83	28·262	·379	1·14115	1·1533												
LEAD	82	27·884	·378	1·17202	1·18352												
THALLIUM	81	27·503	·381	1·20471	1·21603												
MERCURY	80	27·125	·378	1·2385	1·2497												
GOLD	79	26·749	·376	1·27355	1·28489												
PLATINUM	78	26·374	·375	1·31008	1·32121												
IRIDIUM	77	25·997	·377	1·34854	1·35939												
OSMIUM	76	25·621	·376	1·38816	1·3982												
DVI-MANGANESE§	75	25·246	·375	1·4298	1·4408	1·4353	1·2358	1·43	—	1·43	1·233	1·434	1·232			1·428	—
TUNGSTEN	74	24·869	·377	1·47348	1·48452												
TANTALUM	73	24·499	·370	1·51825	1·5294												
HAFNIUM‖	72	24·125	·374	1·56607	1·57704												
LUTECIUM¶	71	23·751	·374	1·61551	1·62636												
* THE HIGHEST MEMBER OF THE MANGANESE GROUP.								OTHER LINES		OTHER LINES		OTHER LINES		OTHER LINES		OTHER LINES	
† ν = FREQUENCY α_1 LINES, RYDBERG'S CONSTANT = 109737 = R.								Mn $K\alpha$ & β		Cu $K\alpha$ & β		Cu $K\alpha$ & β		Cu $K\beta$		Cu $K\alpha$ 1·537	
‡ $10^8/[(\sqrt{\nu/R})^2 \times R]$ = WAVE-LENGTH, λ, IN Å UNITS.								Fe $K\alpha$ & β				Br-Ag Abs.		λ = 1·045		Cu $K\beta$ 1·389	
§ OR RHENIUM.								Cu $K\alpha$ & β						λ = 0·912		λ = 0·950	
‖ OR CELTIUM (Ct).														λ = 0·763		λ = 0·916 Br Ab	
¶ OR CASSIOPEIUM (Cp).																λ = 0·735	
** WIDE STRONG LINE. Br $K\alpha_2$ = 1·04172. Br $K\alpha_1$ = 1·03768.																λ = 0·651	
←--------→ = SAME VALUE ENTERED TWICE.																	

ratio $Ag93O_4$:AgBr, an atomic weight of about 240 was obtained. Koblic hence assumed that he had been successful in isolating the element 93 which he had predicted, and made his report in the chemical journals. He estimated that "bohemium" occurred to the extent of about 1 per cent in pitchblende, which would be a very large quantity of an element which had escaped detection for such a long period of time.

Subsequent x-ray and arc emission spectroscopic analyses failed to confirm the presence of any new element, but the presence of tungsten was unmistakable. Later tungsten was found in the material prepared by Koblic, the analyses having been made by I. Noddack (67). She reported that the preparation was a mixed salt of silver and thallium vanadates and tungstates in an excess of tungstic acid. The erroneous atomic weight obtained was due to the fact that the silver salt thought to be $Ag93O_4$ was in reality a complex silver tungstate. The unusual behavior of tungstates in acid media may be the reason for the observed reactions.

It is to Koblic's (54, 15) credit that he withdrew his claim for the existence of element 93 in the pitchblende.

III. THE NUMBER OF POSSIBLE ELEMENTS

Some of the discussions which have been reported relative to the total number of possible elements should be considered before reviewing the physical and chemical properties that might be expected for the transuranium elements.

In 1889, in his address on "The Chemical Problems of Today," Victor Meyer (65) stated that in order "to cast a glance upon general chemical studies which lie some years behind us, we must, above all, consider one of the most far-reaching discoveries of our epoch, *the revelation of the natural system of the chemical elements.* We owe this to the far-seeing Demetrius Mendeléeff. By the side of the titanic figure of the Russian scholar we see the Englishman, Newlands, and our own countryman, Lothar Meyer, successfully co-operating in the foundation and the structure of this work. What these men created has since become generally known: *they showed that the properties of the elements are functions of their atomic weights.* Mendeléeff taught us to predict the existence and the properties of chemical elements as yet unknown with a certainty. . . . The natural system has imposed upon us a problem of the greatest significance in the new determination of atomic weights, the numerical values of which are now of increased interest. But numerous other problems are presented by the new system of the elements. Above all, we are at a loss to discern the cause of the inner nexus of the elements as the system offers it. Also by diligent work, the less studied elements must be properly brought within the system. Fortunate circumstances may allow us to discover the numerous elements indicated by the periodic law. Here let us note a peculiar coincidence. We know today about seventy elements, but Mendeléeff's table indicates so far two small periods of seven each and five large ones of seventeen elements respectively. To these must be added hydrogen forming a 'group' in itself.

"By addition of these figures, 2 × 7 + 5 × 17 + 1, we obtain exactly the number 100.

"It is true that no one can say whether the missing elements will really be discovered or if further new periods might not be indicated by which this number, 100, would be exceeded. But as far as positive data are at hand, they indicate exactly the number mentioned and nothing points beyond it. An odd coincidence which seems to ally the number of the existing elements with the number of our fingers."

This prediction of Victor Meyer's has not been exceeded. However, since then has come the discovery of the rare gases and of the radioactive elements. Moseley's law has permitted the determination of the number of rare earth elements that should be expected. The concept of isotopes has also entered the picture. All of these ideas have affected scientific thought, leading ultimately to the development of the Bohr theory and the different wave and quantum mechanics which have been the vogue during the past two decades.

The expounding of the Bohr theory brought forth several reports on the total possible number of elements. This was probably due in part to the new theory, and in part to the fact that investigators, following the discovery of both the electron and radioactivity, had called attention to the possibility that radioactive disintegration might be due to disturbing effects of the electrons around the atom, since ordinary mechanics and electrodynamics failed to account for radioactive decay. On the basis of the quantum postulates and the Bohr atom, Rosseland (71) attempted to show that in uranium the electrons in the first quantum group are located at a very short distance from the nucleus. In other words, for uranium, the constantly increasing attraction by the nucleus and the progressive repulsion set up by the increase in the number of electrons in the atom causes a contraction of the innermost electronic orbits so that they approach, in size, the order of magnitude of the nucleus itself, namely about 1.1^{-13} cm. Any further attraction of the innermost electrons would then cause them to be brought inside the nucleus. Rosseland, using certain of the concepts of the Bohr theory, attempted to show that this relationship existed at atomic number 92.

Another approximate upper limit can be determined by Bohr's method, which depends upon a peculiarity of the relativistic energy levels of the hydrogen atom. The inner electrons of a heavy atom are supposed to be hydrogenic, so the equation

$$1 + \frac{E}{mc^2} = \left(1 + \frac{\alpha^2 Z^2}{[n_r + (k^2 - \alpha^2 Z^2)^{\frac{1}{2}}]^2}\right)^{-\frac{1}{2}}$$

may be derived. In the term $(k^2 - \alpha^2 Z^2)^{\frac{1}{2}}$ of this expression, when the term Z becomes sufficiently large an imaginary number results. At that point, therefore, a stable grouping could no longer persist. When $n = 1$ and $Z = 137$, this condition is fulfilled, indicating that no atom of atomic number greater than 137 can exist.

This method of calculation has been criticized on the basis that modifications of the laws of force must be considered when such small distances are involved. Kossel (55) assumed that the magnetic attraction of two electrons is proportional to r^{-4} and the electrostatic repulsion to r^{-2}. This indicates again that should the K-orbit become too small, an electron might fall into the nucleus, reducing the nuclear charge.

Similar calculations made by Flint and Richardson (37), on the basis of certain considerations of relativistic mechanics, indicated that there is a minimum possible radius for a circular inner electronic orbit, this limit being reached when $Z = 98$.

Erwin Meyer (64) discussed, in 1927, the limits of the periodic system with notations as to the results of other investigators. Using the older concept that electrons were located in spheres around the nucleus and that the radii of the spheres were proportional to the squares of the quantum numbers, he pointed out that the sum of the squares of the numbers from 1 to 6, thus $1 + 4 + 9 + 16 + 25 + 36$, gives the number 91. Then by including also the second electron of helium, which he stated was associated with the hydrogen electron in the innermost sphere, one obtains the number 92 as the limit of the atomic series. Uranium then would have, according to his concept, a nucleus with six surrounding shells. After an explanation of his point of view, he went on to say "that a hyperuranium or eka-uranium has no place in the periodic system and that the highest atomic number of 92 is no accidental number."

Von Weinberg (79), in an article entitled "On the Origin of the Chemical Elements," stressed the point that the building-up process of the elements proposed by Bohr does not consider uranium as being the natural limit in the series of the chemical elements, but that one can on the contrary predict the properties of elements which are still heavier, should they exist.

Calculations and important contributions have been made by Eddington, Bohr, Sommerfeld, and many other scientists in attempting to solve the puzzle of the possible number of elements. Many of them have found that the number 137 satisfies the conditions for the ultimate breaking down of the atomic system. This number has, as a result, become a magic number in discussions of this problem.

It is seen therefore that the ideas as to the total number of possible elements are variant, the suggested values ranging from 92 to 137. It was the thought that transuranium elements may exist, at least hypothetically, that furnished one of the motives in the attempt to produce transuranium elements by bombardment with particles of high energy.

IV. PROPERTIES OF THE TRANSURANIUM ELEMENTS

A. Possible electronic configurations

With these ideas in mind, perhaps the next logical step is to consider the properties which might be predicted for the transuranium elements. In simple fashion this could be done by studying one of a number of different forms of the periodic classification and predicting properties for the elements. On the other hand, if tables of electronic configurations are studied first, it becomes possible to indicate the most probable structure for the atoms, and hence the most likely manner in which the elements beyond uranium may be arranged in a periodic table.

Naturally no spectroscopic data are available, a fact which also holds true for several of the other elements listed in the natural radioactive series. Any proposed scheme of electronic configuration for elements beyond element 92 must be pure conjecture, but these conjectures should permit a fairly accurate estimate of the properties of the elements.

The first question is that of deciding what might be the atomic number of the next rare gas. After that value has been chosen it is possible to arrange the elements for the series between radon and the "hypothetical rare gas" in various combinations and to guess the most probable arrangement.

One method of estimating the atomic number of the next rare gas is to apply Rydberg's rule, even though there is no definite evidence to show that it might hold for elements beyond uranium. This generalization gives the atomic number of the rare gases as equal to twice the sum of the squares of the ordinal numbers, 1, 2, 3, etc. For helium it is 2×1^2; for neon, $2(1^2 + 2^2)$ or 10; for argon, $2(1^2 + 2^2 + 2^2)$ or 18; and so on, until for radon it is $2(1^2 + 2^2 + 2^2 + 3^2 + 3^2 + 4^2)$ or 86. Should this series continue in this same manner, then the atomic number of the next "rare gas" would be determined by the series $(1^2 + 2^2 + 2^2 + 3^2 + 3^2 + 4^2 + 4^2)$ and would be 118.

A second method of arriving at this same number would be to observe the regularities in the electronic configurations for the rare gases. All of these elements have two electrons in the K-orbit. With the exception of helium, all the known rare gases have eight electrons in the outer completed orbit, and eight in the second or *L*-orbit. The other orbits possess either eighteen or thirty-two electrons. Table 2 gives the electronic configurations for the known rare gases as well as for the hypothetical element No. 118. The last value was determined in this instance by assuming that the repetition of 32 would follow for this last rare gas, in exactly the same fashion that 8 and 18 had repeated in the earlier sequences. This indicates, therefore, that the next series in a periodic classification would consist of the same number of elements as the series beginning with cesium.

The next question is to decide how the elements between element 86, radon, and element 118 should be arranged in a periodic classification. The series beginning with cesium consists of thirty-two elements and includes the very interesting group of the rare earth elements. The series beginning with radon likewise would have thirty-two elements. It might also have a new "rare earth" group.

TABLE 2

Electronic configurations of the rare gases

GAS		*K*	*L*	*M*	*N*	*O*	*P*	*Q*
He	2	2						
Ne	10	2	8					
A	18	2	8	8				
Kr	36	2	8	18	8			
Xe	54	2	8	18	18	8		
Rn	86	2	8	18	32	18	8	
?	118	2	8	18	32	32	18	8

In the accompanying tables of electronic configurations (tables 3 and 4), it is seen that transition groups occur with the elements 21 to 28 and 39 to 46, inclusive. In these instances it is obvious that the building-up process is not occurring in the outermost electronic group but rather one shell deeper in the atom. It is also observed that the same sort of change begins to take place beginning with lanthanum, No. 57, and ends with platinum, No. 78, which is a homolog of palladium, No. 46. However, there is one very striking difference in this series of elements. *First*, the series is longer than any of the preceding. *Second*, beginning with cerium, No. 58, the newly added electrons do not take their places in either of the outer two electronic groups, but rather fall into a shell lying deeper within the atom, namely the 4*f* shell. This type of change, in which an inner electronic group is being completed, gives rise to what is known as an "inner transition group." This building up of an inner electronic group as indicated affords an explanation for the very definite similarities in the

TABLE 3 (PART 1)

Electron configurations and term types for the ground states of the elements

(Numbers and symbols in parentheses are uncertain)

ELEMENT	K	L		M			N				O					GROUND TERM
	1s	2s	2p	3s	3p	3d	4s	4p	4d	4f	5s	5p	5d	5f	5g	
1. H	1															$^2S_{1/2}$
2. He	2															$^1S_0$
3. Li	2	1														$^2S_{1/2}$
4. Be	2	2														$^1S_0$
5. B	2	2	1													$^2P_{1/2}$
6. C	2	2	2													$^3P_0$
7. N	2	2	3													$^4S_{3/2}$
8. O	2	2	4													$^3P_2$
9. F	2	2	5													$^2P_{3/2}$
10. Ne	2	2	6													$^1S_0$
11. Na	2	2	6	1												$^2S_{1/2}$
12. Mg	2	2	6	2												$^1S_0$
13. Al	2	2	6	2	1											$^2P_{1/2}$
14. Si	2	2	6	2	2											$^3P_0$
15. P	2	2	6	2	3											$^4S_{2/2}$
16. S	2	2	6	2	4											$^3P_2$
17. Cl	2	2	6	2	5											$^2P_{3/2}$
18. A	2	2	6	2	6											$^1S_0$
19. K	2	2	6	2	6		1									$^2S_{1/2}$
20. Ca	2	2	6	2	6		2									$^1S_0$
21. Sc	2	2	6	2	6	1	2									$^2D_{3/2}$
22. Ti						2	2									$^3F_2$
23. V						3	2									$^4F_{3/2}$
24. Cr						5	1									$^7S_3$
25. Mn						5	2									$^6S_{5/2}$
26. Fe						6	2									$^5D_4$
27. Co						7	2									$^4F_{9/2}$
28. Ni						8	2									$^3F_4$
29. Cu	2	2	6	2	6	10	1									$^2S_{1/2}$
30. Zn							2									$^1S_0$
31. Ga							2	1								$^2P_{1/2}$
32. Ge							2	2								$^3P_0$
33. As							2	3								$^4S_{3/2}$
34. Se							2	4								$^3P_2$
35. Br							2	5								$^2P_{3/2}$
36. Kr							2	6								$^1S_0$
37. Rb	2	2	6	2	6	10	2	6			1					$^2S_{1/2}$
38. Sr	2	2	6	2	6	10	2	6			2					$^1S_0$
39. Y	2	2	6	2	6	10	2	6	1		2					$^2D_{3/2}$
40. Zr									2		2					$^3F_2$
41. Cb									4		1					$^6D_{1/2}$
42. Mo									5		1					$^7S_3$
43. Ma									(5)		(2)					$(^6S_{5/2})$
44. Ru									7		1					$^5F_5$
45. Rh									8		1					$^4F_{9/2}$
46. Pd									10							$^1S_0$
47. Ag	2	2	6	2	6	10	2	6	10		1					$^2S_{1/2}$
48. Cd											2					$^1S_0$
49. In											2	1				$^2P_{1/2}$
50. Sn											2	2				$^3P_0$
51. Sb											2	3				$^4S_{3/2}$
52. Te											2	4				$^3P_2$
53. I											2	5				$^2P_{3/2}$
54. Xe											2	6				$^1S_0$

TABLE 3 (PART 2)

Electron configurations and term types for the ground states of the elements
(Numbers and symbols in parentheses are uncertain)

ELEMENT	K	L	M	N				O					P						Q	GROUND TERM
				4s	4p	4d	4f	5s	5p	5d	5f	5g	6s	6p	6d	6f	6g	6h	7s	
55. Cs	2	8	18	2	6	10		2	6				1							$^7S_{1/2}$
56. Ba	2	8	18	2	6	10		2	6				2							$^1S_0$
57. La	2	8	18	2	6	10		2	6	1			2							$^2D_{3/2}$
58. Ce	2	8	18	2	6	10	(1)	2	6	(1)			(2)							$(^3H_4)$
59. Pr							(2)	2	6	(1)			(2)							
60. Nd							(3)	2	6	(1)			(2)							
61. Il							(4)	2	6	(1)			(2)							
62. Sm							6	2	6				2							$^7F_0$
63. Eu							7	2	6				2							$^8S_{7/2}$
64. Gd							7	2	6	1			2							^9D
65. Tb							(8)	2	6	(1)			(2)							
66. Dy							(9)	2	6	(1)			(2)							
67. Ho							(10)	2	6	(1)			(2)							
68. Er							(11)	2	6	(1)			(2)							
69. Tm							13	2	6				2							$^2F_{7/2}$
70. Yb							14	2	6				2							$^1S_0$
71. Lu	2	8	18	2	6	10	14	2	6	1			2							$^2D_{3/2}$
72. Hf								2	6	2			2							$^3F_2$
73. Ta								2	6	3			2							$^4F_{3/2}$
74. W								2	6	4			2							$^5D_0$
75. Re								2	6	5			2							$^6S_{5/2}$
76. Os								2	6	6			2							$^5D^4$
77. Ir								2	6	7			2							^4F
78. Pt								2	6	9			1							$^3D_3$
79. Au	2	8	18	2	6	10	14	2	6	10			1							$^2S_{1/2}$
80. Hg													2							$^1S_0$
81. Tl													2	1						$^2P_{1/2}$
82. Pb													2	2						$^3P_0$
83. Bi													2	3						$^4S_{3/2}$
84. Po													2	4						$^3P_2$
85. —													2	5						$^2P_{3/2}$
86. Rn													2	6						$^1S_0$

chemical and physical properties of the rare earth elements, of which this inner transition group is composed. It explains also the "lanthanide contraction," which in turn may be used to explain the similarity of properties of elements 72 to 78 with those of the elements which are their lower homologs, numbers 40 to 46, respectively.

TABLE 4

A possible electronic configuration for elements 86 to 118

ELEMENT	K	L	M	N				O				P				Q	
				4s	4p	4d	4f	5s	5p	5d	5f	6s	6p	6d	6f	7s	7p
86. Rn.....	2	8	18	2	6	10	14	2	6	10		2	6				
87.	2	8	18	2	6	10	14	2	6	10		2	6			1	
88. Ra......	2	8	18	2	6	10	14	2	6	10		2	6			2	
89. Ac......	2	8	18	2	6	10	14	2	6	10		2	6	1		2	
90. Th.....	↑	↑	↑											2		2	
91. Pa......														3		2	
92. U.......														4		2	
93. E-Re...														5		2	
94. E-Os....														6		2	
95. E-Ir....														7		2	
96. E-Pt....														9		1	
97. E-Au...												2	6	10		1	
98. E-Hg...												2	6	10		2	
99.						32			18		1	2	6	10		2	
100.											2					2	
101.											3					2	
102.											4					2	
103.											5					2	
104.											6					2	
105.											7					2	
106.											8					2	
107.											9					2	
108.											10					2	
109.											11					2	
110.											12					2	
111.											13					2	
112.								2	6	10	14					2	
113.																2	1
114.																2	2
115.																2	3
116.																2	4
117.	↓	↓	↓													2	5
118. E-Rn...	2	8	18	2	6	10	14	2	6	10	14	2	6	10		2	6

For the period beginning with element 87, ekacesium, there is again the possibility of a recurrence of a transition group exactly similar to those of the preceding periods. Since the number of elements in this period is postulated as the same for the series beginning with cesium, the important question at this point is whether there will be an "inner transition group" similar to the rare earth group. A definite answer in this case will naturally depend on the energy relationships for the addition of electrons to the various shells, and as yet there is positively no information to establish this point.

Referring to the electronic configuration tables, it is noted that calcium has two electrons in the 4*s* orbit. Magnesium, likewise, has two electrons in its outermost orbit. Should the building-up process continue beyond calcium, as it did in the case of magnesium, the new electrons should drop into the 4*p* shell. However, the energy relationships calculated from spectroscopic data show that the electrons go into the 3*d* shell for the elements scandium to nickel. These elements make up the transition group whose properties are somewhat more similar than those of the other members of this series. The elements gallium to krypton constitute the group where the electrons are again adding to the outer or 4*p* shell, the rare gas configuration being completed with krypton.

In the next period an exactly similar situation exists. The electrons are first added, for rubidium and strontium, to the 5*s* shell. With yttrium, however, the next electron adds to the 4*d* and not to the 5*p* shell. The elements yttrium to palladium make up this second transition group. The 5*p* electrons are added from indium to xenon, which is the rare gas completing this period.

In the next period, exactly the same sort of change starts to take place. For cesium and barium the electrons are added in the outermost or 6*s* group. For lanthanum the energy relationship is such that the third electron being added drops into the 5*d* instead of into the 6*p* group. This is analogous to the preceding groups.

However, with cerium a new type of change occurs. The electron which is being added to the structure in this case does not drop into either the 6*p* or the 5*d* shell but rather deeper into the atom, namely, into the 4*f* shell. This addition of electrons to the 4*f* shell continues until that group is completed with fourteen electrons. With lutecium we have again a structure analogous to that shown by yttrium, in that the innermost orbital groups are all completed, namely, the *K*, *L*, and *M* groups for yttrium and the *K*, *L*, *M*, and *N* groups for lutecium.

The elements cerium to ytterbium are known as an "inner transition" group. The very definite similarities in the chemical and physical properties of the rare earth elements are due to this change in electronic structure which is taking place deeper in the atom, and to the fact that the outermost electronic configurations, which define the valence relationships, are essentially identical. The "lanthanide contraction," often used to explain the similarities in the properties of the elements in this portion of the atomic series, is due to this electronic change occurring in the 4*f* shell rather than in the outer portion of the atom.

Following the rare earth group the changes again take place in the outer orbital groups, as was the case in the previous periods, the normal transition group ending with platinum, the higher homolog of palladium.

With the beginning of the series starting immediately after radon, with ekacesium, No. 87, the question arises relative to the occurrence of an "inner transition" group before the next rare gas. As outlined above, it is assumed that the next rare gas configuration will be attained with element 118. For those energy relationships which have been determined, this period begins in exactly the same fashion as all of the preceding, that is, the first two electrons go into the outermost electronic group, the 7*s* in this instance. The evidence also indicates that the next electrons are added to the 6*d* shell and not to the 7*p* shell. This is analogous to the first two transition periods. This type of structure probably holds as far as uranium, although spectroscopic data for this portion of the atomic series are far from being complete. Therefore, anything that is said about this portion of the table is, to a great extent, mere conjecture.

At this point the question of another "inner transition" group built up in a fashion like the rare earth group must be considered. One should ask whether such a transition group might begin with thorium. This element occupies a position in this last period similar to that of cerium in the preceding group. Likewise one might think such a group could begin with ekarhenium, just following uranium. Perhaps the transition group would occur later in the atomic series, and perhaps not at all.

In the transition groups it is observed that, after two or three electrons become associated with a group, their presence tends to stabilize that particular structure; additional electrons then tend to add to that same orbital group until a completed shell is formed. This is the case with the 3*d* electrons for the group beginning with scandium, the 4*d* electrons following yttrium, and the 4*f* electrons for the rare earth elements. Following actinium (No. 89) and up to uranium (No. 92), the meager amount of spectroscopic data available seems to indicate that the electrons are adding to the 6*d* shell rather than dropping deeper into the atom. Might it not be logical to think that, because of the stabilizing influence of these first three or four electrons, the electrons shall continue to take their places in this 6*d* orbital grouping until it is completely filled? If such should be the case, then a normal transition group would begin with actinium and end with ekaplatinum (No. 96). From this point of view, therefore, consideration of a new "inner transition" group early in this period is eliminated. It does not eliminate the possibility of a second "inner transition" group at a later point in the atomic series. Comparison of tables 3 and 4 shows the very decided difference in the type of structure of these super-heavy atoms with respect to the location of the inner transition or "rare earth type" elements.

Two Bohr–Thomsen tables are given here for comparison. One of these is that proposed by Bohr (table 8), in which it is indicated that an inner transition group analogous to the rare earth group begins with element 94. The other (table 7) has been drawn up according to the above conjecture, which obviously may be entirely wrong, since so little is known of the energy relationships which might be expected in this proposed portion of the atomic series.

The building-up process continues, as indicated in the table of electronic configurations (table 4), so that the 7*s* and 6*d* electrons are added first. Elements 97 and 98 are assigned structures which are analogous to those of gold and mercury. With element 99 the next electron to be added is placed in the 5*f* group. The 6*s*, 6*p*, and 6*d* and 7*s* shells remain as they were. Electrons are added continuously to the 5*f* shell, analogous to the filling in of the 4*f* electrons in the rare earths. Thus an "inner transition group" is being built up, similar to the rare earths in that the electrons are added to an inner electronic group but different in that it is not part of an ordinary transition group which has already been started.

To be sure, the chemical and physical properties of elements 99 to 112 would be very similar, and probably like ekamercury, number 98. Their properties will be summarized later, in a discussion of two different types of the periodic table, one of which will correspond to this type of electronic configuration. With element 113, electrons again should add to the outermost electronic grouping, giving the elements analogous to the series thallium to radon, respectively. This change would end with No. 118, the next (hypothetical) rare gas.

B. *Periodic classifications including the transuranium elements*

In considering all possible arrangements several periodic tables were prepared, four of which are reproduced here. Two of these (tables 5 and 7) correspond to the electronic configuration proposed above (table 4), whereas the other two (tables 6 and 8) correspond to an arrangement where the "inner transition" group is a portion of a normal transition group. In these last two tables the "inner transition" group begins with ekaosmium ($Z = 94$).

These periodic classifications permit the preparation of a summary of the physical and chemical properties of the elements beyond uranium in

TABLE 5

A periodic classification which corresponds to the electronic configuration given in table 4 (see table 6)

																H 1	He 2
Li 3	Be 4											B 5	C 6	N 7	O 8	F 9	Ne 10
Na 11	Mg 12											Al 13	Si 14	P 15	S 16	Cl 17	A 18
K 19	Ca 20	Sc 21	Ti 22	V 23	Cr 24	Mn 25	Fe 26	Co 27	Ni 28	Cu 29	Zn 30	Ga 31	Ge 32	As 33	Se 34	Br 35	Kr 36
Rb 37	Sr 38	Y 39	Zr 40	Cb 41	Mo 42	Ma 43	Ru 44	Rh 45	Pd 46	Ag 47	Cd 48	In 49	Sn 50	Sb 51	Te 52	I 53	Xe 54
Cs 55	Ba 56	*	Hf 72	Ta 73	W 74	Re 75	Os 76	Ir 77	Pt 78	Au 79	Hg 80	Tl 81	Pb 82	Bi 83	Po 84	Ab 85	Rn 86
V 87	Ra 88	Ac 89	Th 90	Pa 91	U 92	E-Re 93	E-Os 94	E-Ir 95	E-Pt 96	E-Au 97	☒	113	114	115	116	117	118
*Rare Earths:			La 57	Ce 58	Pr 59	Nd 60	Il 61	Sm 62	Eu 63	Gd 64	Tb 65	Dy 66	Ho 67	Er 68	Tm 69	Yb 70	Lu 71
☒	Possible Transition Group		E-Hg 98	99	100	101	102	103	104	105	106	107	108	109	110	111	112

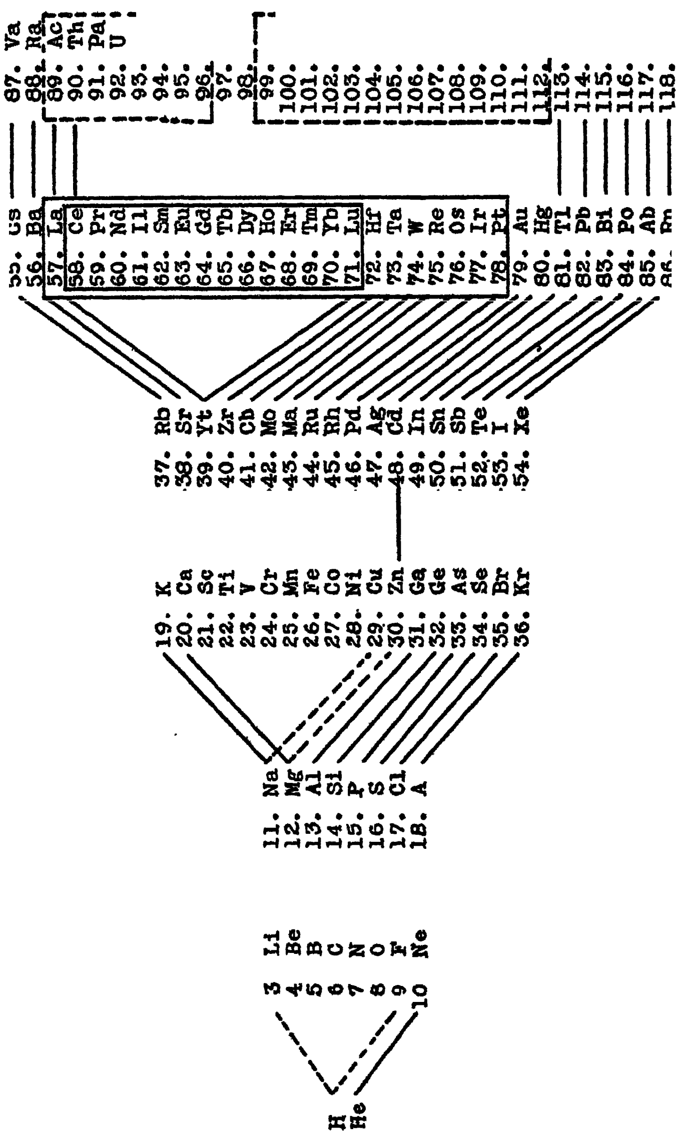
TABLE 6

A long-type periodic table with an "inner transition" group within a normal transition group (see table 8)

																H 1	He 2
Li 3	Be 4											B 5	C 6	N 7	O 8	F 9	Ne 10
Na 11	Mg 12											Al 13	Si 14	P 15	S 16	Cl 17	A 18
K 19	Ca 20	Sc 21	Ti 22	V 23	Cr 24	Mn 25	Fe 26	Co 27	Ni 28	Cu 29	Zn 30	Ga 31	Ge 32	As 33	Se 34	Br 35	Kr 36
Rb 37	Sr 38	Y 39	Zr 40	Cb 41	Mo 42	Ma 43	Ru 44	Rh 45	Pd 46	Ag 47	Cd 48	In 49	Sn 50	Sb 51	Te 52	I 53	Xe 54
Cs 55	Ba 56	*	Hf 72	Ta 73	W 74	Re 75	Os 76	Ir 77	Pt 78	Au 79	Hg 80	Tl 81	Pb 82	Bi 83	Po 84	Ab 85	Rn 86
V 87	Ra 88	Ac 89	Th 90	Pa 91	U 92	E-Re 93	☒	109	110	111	112	113	114	115	116	117	118
*Rare Earths:			La 57	Ce 58	Pr 59	Nd 60	Il 61	Sm 62	Eu 63	Gd 64	Tb 65	Dy 66	Ho 67	Er 68	Tm 69	Yb 70	Lu 71
☒ Possible Transition Group			E-Os 94	95	96	97	98	99	100	101	102	103	104	105	106	107	108

TABLE

Bohr–Th n tab ina to the onfi le

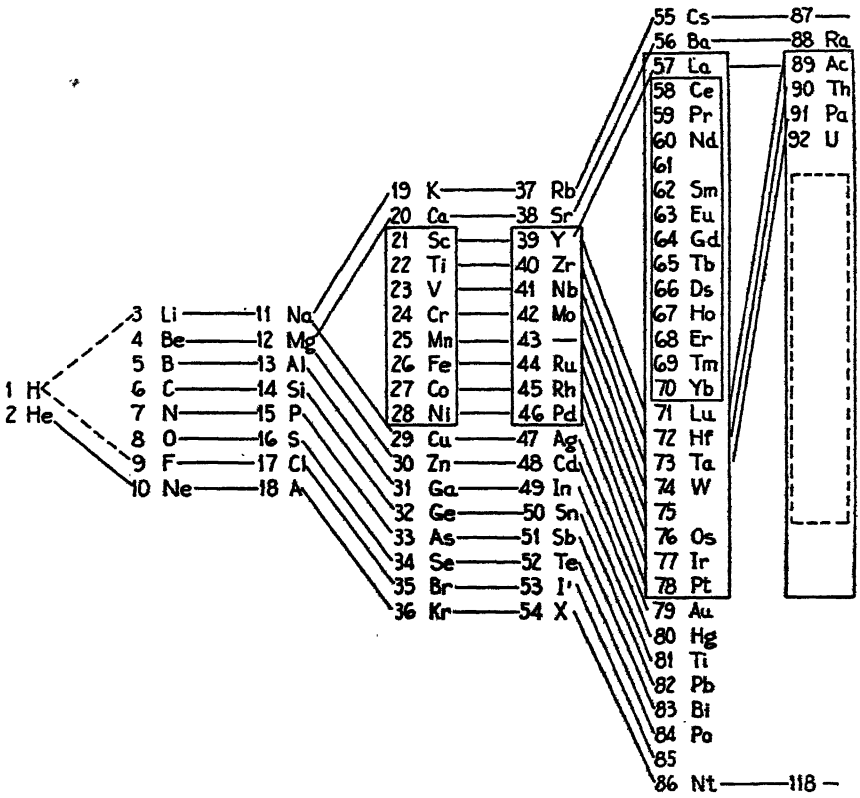


the atomic series. The only possibilities to be considered here will be the following: (*1*) Elements 87 to 118 as a period, with elements 94 to 108 as an "inner transition" group; and (*2*) elements 87 to 118 as a period, with elements 98 to 112 as an "inner transition" group.

Recently von Grosse (76) has written regarding the expected chemical properties of elements 93 and 94. He considered two possibilities,—one with elements 93 and 94 as homologs of rhenium and osmium, the other with a new "inner transition" group beginning with uranium as the first member, just as cerium is the first member of the rare earth group in the previous period.

TABLE 8

A Bohr-Thomsen table with an "inner transition" group within a normal transition group



With respect to the first possibility, von Grosse states, "Ekarhenium (En) will have a valency from a maximum of 7 down to 2 and even 1. The highest oxide, En_2O_7, will be stable, like Re_2O_7, and unlike Mn_2O_7; it will be volatile and probably sublime or melt below 375°. Hydrogen will reduce it at elevated temperatures first to lower, non-volatile oxides and later probably to the metal itself. It will form in water solution the acid,

$HEnO_4$, with water-soluble salts like $KEnO_4$, $Ba(EnO_4)_2$, etc. Since the basicity increases with the period number, $HEnO_4$ must also be basic enough to form water-soluble salts with strong acids (HNO_3, HCl, etc.), analogous to uranyl salts. In any case it will remain in solution in highly acid media. Ekarhenium hexa- or hepta-fluoride (EnF_7) will be very volatile and will be immediately hydrolyzed by water into HF and hydrated oxides.

"Ekaosmium will also have different valences, 8 being the highest. The highest oxide—the tetroxide, $EOsO_4$—will sublime and boil below 200°, dissolve in water and alkalies similarly to OsO_4, but will be a weaker oxidizing agent than OsO_4.

"The highest halides, especially the fluorides, will be volatile and readily hydrolyzable."

The above properties were derived on the basis of an electronic configuration as given in table 9. With respect to the second possibility, which is in accordance with the Bohr theory that "a second group of rare elements" exists, von Grosse gives the electronic configurations shown in table 10, and states that "we may assume that the filling of this lower quantum level has begun already in uranium; in this case the electron distribution would be given by Table III (i.e., table 10) according to the most reliable present knowledge.

"Uranium would then correspond to cerium in the first group of rare earths and elements 93 and 94, also 95 and 96, etc., would all have properties very similar to element 91, just as the chemical properties of Pr, Nd, Sm, etc., are practically identical with La, and elements 93, and 94 in that case, would *not have* the properties of ekarhenium and ekaosmium.

"It might also be that the filling up of the n_5 quantum level will begin at element 93, or 94, or even later; in the first case element 93 will be similar to uranium, just as Ce resembles La, and only in special cases resemble rhenium (like Ce → Zr). A definite decision as to the real nature of these elements could be made after calculating the energy levels of the transuranium elements."

Naturally, as von Grosse also states, if the energy levels of the last three elements in the periodic table (thorium, protoactinium and uranium) were known exactly, it would be possible to predict with more certainty what the behavior of the transuranium elements should be.

1. Elements 87 to 118 as a period, with elements 94 to 108 as the transition group

(*a*) The chemistry of elements 87 to 92 does not need to be considered.

(*b*) *Element 93, ekarhenium.* (*1*) Ekarhenium should exhibit valences from 7 down to 1 or 2. (*2*) The highest oxide of element 93 should be more stable than Re_2O_7; it should be definitely unlike Mn_2O_7 it; should be

TABLE 9*

Electronic configurations of elements 91, 92, 93, and 94

(The electron distribution of the elements given is based on the analogy with their lower homologs)

QUANTUM NUMBERS n.......	1	2		3			4				5				6				7	HIGHEST VALENCY
l.......	*s*	*s*	*p*	*s*	*p*	*d*	*s*	*p*	*d*	*f*	*s*	*p*	*d*	*f*	*s*	*p*	*d*	*f*	*s*	
ELEMENTS																				
91 Et	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6	3		2	5
92 U	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6	4(5)		2(1)	6
93 En	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6	5(6)		2(1)	7
94 Eo	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6	6(7)		2(1)	8

ulated by von Gro

TABLE 10*

Electronic configurations according to the Bohr theory

QUANTUM NUMBERS n.......	1	2		3			4				5				6				7	HIGHEST VALENCY
l.......	*s*	*s*	*p*	*s*	*p*	*d*	*s*	*p*	*d*	*f*	*s*	*p*	*d*	*f*	*s*	*p*	*d*	*f*	*s*	
ELEMENTS																				
91 Et	2	2	6	2	6	10	2	6	10		2	6	10		2	6	3		2	5
92 U	2	2	6	2	6	10	2	6	10		2	6	10	1	2	6	4		1	6
93	2	2	6	2	6	10	2	6	10		2	6	10	2(1)	2	6	4(5)		1	5(6)
94	2	2	6	2	6	10	2	6	10		2	6	10	3	2	6	4		1	5
95	2	2	6	2	6	10	2	6	10		2	6	10	4	2	6	4		1	5
etc.																				

* Formulated by von Grosse (76).

definitely volatile, subliming or melting between 300–400°C. This oxide should be easily reduced to lower oxides and then to the metal. (*3*) Ekarhenium would probably be placed along with arsenic or bismuth in the electromotive force series table. (*4*) The chlorides of higher valence should be more stable than those of rhenium, and very definitely more stable than the higher chlorides of manganese. They should be volatile at moderate temperatures. (*5*) The sulfide should form in acid solution in an analogous fashion to ReS_2. (*6*) The metal should dissolve in aqua regia, nitric acid, or other strong oxidizing media to give the acid, $HEnO_4$. (*7*) The element probably would be radioactive.

(*c*) *Element 94.* This element should be somewhat similar in behavior to osmium and should be designated as ekaosmium. It would be the first member of a new inner transition group. (*1*) Like osmium, element 94 might exhibit a valence of 8 as a maximum. (*2*) Its oxide, $94O_4$ should be very volatile, and could probably be steam-distilled from an acid medium. The oxide should react with water to form an acid, and with alkalies. It should be a weaker oxidizing agent than OsO_4. (*3*) The highest halides should be volatile and hydrolyzable. (*4*) The metal should be obtained by reduction more easily than osmium. (*5*) The element should be placed below osmium in the electromotive force series table. Hence platinum and gold should displace it easily from solution. (*6*) The element should form a sulfide in acid solution in similar fashion to rhenium, ekarhenium, osmium, and platinum. (*7*) The metal should have a relatively high melting point, probably about 2000°C. (*8*) If existent in nature, the element should probably be in the free form or as an alloy with other precious metals.

(*d*) *Elements 95 to 108.* (*1*) These elements should all be very similar in properties to ekaosmium, hence their properties would be analogous to those mentioned in the preceding section. The chief differences would be of degree. All of them would probably exhibit a maximum valency of 8. Each of the elements should form higher oxides which would be reasonably volatile, and would differ sufficiently so that separations could be effected. The separations would be difficult. (*2*) The elements should stand below platinum in the electromotive force series. (*3*) They should form compounds like the chloroösmiates, with the probability that perhaps eight groups might be coördinated. (*4*) Undoubtedly, there would be a shrinkage in atomic and ionic sizes of these elements analogous to the "lanthanide contraction" in the rare earth group. This would mean that the properties of the members of this group and of the elements immediately following would vary in a fashion somewhat similar to the changes noted for the rare earths and the elements following (hafnium, tantalum, etc.).

(*e*) *Elements 109 to 110.* These would be homologs of iridium and platinum. Should a contraction of atomic and ionic sizes take place, analogous to the "lanthanide contraction," these elements should be very similar to iridium and platinum in chemical properties, but very different in physical properties such as density, melting point, etc.

(*f*) *Elements 111 to 118.* These would be analogs of the elements gold to radon, respectively. Their properties should be like those of the elements of the previous period (gold, mercury, . . . radon), because of the volume contraction mentioned above. (Zirconium and hafnium, columbium and tantalum, etc., are closely related for the same reason.)

2. Elements 87 to 118 as a period, with elements 89 to 97, inclusive, as a normal transition group, and elements 98 to 112 as an "inner transition" group

This arrangement corresponds to the electronic configurations given in table 4 and in the periodic tables (tables 5 and 7). This particular grouping differs from the preceding in that the "inner transition" group does not build up until after the normal transition group has been completed. Hence, there is a marked difference from the rare earth group, which is an "inner transition" within a normal transition group.

Summarizing this arrangement, it is seen that (*a*) elements 87 to 92 are the elements ekacesium to uranium. (*b*) Element 93 would be a homolog of rhenium, or ekarhenium; element 94 would be a homolog of osmium, or ekaosmium; element 95 would be a homolog of iridium, or ekairidium; element 96 would be a homolog of platinum, or ekairidium. The normal transition group would end at this point. (The transition would begin with No. 89, actinium.) Element 97 would be a homolog of gold, or ekagold. (*c*) Elements 98 to 112 would be an inner transition group, all of the elements having very similar properties. (*d*) Elements 113 to 118 would be analogs of the elements from thallium to radon, respectively.

(*a*) *Elements 87 to 92*, inclusive, are the elements ekacesium, radium, actinium, thorium, protoactinium, and uranium. It will not be necessary to comment on their properties.

(*b*) *Element 93.* The properties of this element would be as listed above (see section 1(b)).

Element 94. The properties of this element would be as listed above (see section 1(c)). The essential *difference* from the preceding case (page 108) is that there would not be a group of fifteen elements possessing very similar properties analogous to ekaosmium.

(*c*) *Elements 95 to 97.* These elements are analogs of iridium, platinum, and gold. They would differ from iridium, platinum, and gold, just as these differ from ruthenium, rhodium, and palladium.

(*d*) *Elements 98 to 112.* These elements form an inner transition group. Ekamercury would be the first member. It would be followed by fourteen elements of very similar properties. All of these elements should be very noble in character, being liquids or low-melting solids. The second member would probably show valences of 2 and 3, and the others would have a normal valence of 2. Regularities within the group would show other valence relationships. A contraction of ionic and atomic volumes would undoubtedly occur with increasing atomic number.

(*e*) *Elements 113 to 118.* These elements are analogs of thallium to radon, respectively. Their properties would be very similar to those of thallium, etc.

(*f*) All of these elements might exhibit radioactivity.

V. ARTIFICIAL RADIOACTIVITY STUDIES ON URANIUM

Previous to 1934 experiments on artificial disintegration had always been considered negative in *two important respects*. *First,* the emission of high energy electrons as disintegration products had not been demonstrated. *Second,* evidence for the persistence of transformation processes after the removal of the source of bombarding particles had been noted. In 1933 and 1934 I. Curie and Joliot (17) reported that in an artificial disintegration the product atom need not always be a stable isotope, but that disintegration could occur with a relatively long mean-life and with the emission of light particles. As bombarding particles, they used the alpha particles from polonium. They found that the ejected particle usually was a positron. Similar results were obtained by other investigators when various elements were bombarded either with alpha particles or with artificially accelerated protons and deuterons.

Fermi reasoned, however, that neutrons should be very effective as bombarding particles, since the effect of Coulomb repulsion, an important factor in the use of charged particles for bombardment, should not be a deterring factor. Accordingly, he, with his associates, Amaldi, D'Agostino, Rasetti, and Segrè, proceeded to bombard systematically the various chemical elements with neutrons. In 1934 Fermi (27, 28, 29) made the first announcement that artificial radioactivity can be produced by neutron bombardment. Essentially his method consisted in using sealed glass tubes about 6 mm. in diameter and 15 mm. in length and containing radon and beryllium powder as a source of neutrons. The neutrons, passing through the glass walls, acted upon either the elements or the compounds containing them, placed about the radon–beryllium mixture.

Since the nuclei of the heavy radioactive elements exhibit a general instability, Fermi (8) deemed it advisable, as part of his investigation, to determine the effect of neutrons on thorium and uranium. It was found that the two elements could be very strongly activated, and the decay curves indicated that the nature of the induced radioactivity was rather complex. For thorium the initial experiments showed the presence of at least two active substances, one of a period less than 1 min., and the other of a period of about 15 min. With uranium the results were rather startling. The decay curves indicated that the several active constituents were present. The appearance of several half-life periods suggested either that the induced activity was due to different isotopic constituents of the element, or that, if only a single isotope was present, either alternative or successive disintegrations were occurring. Likewise the presence of these substances of different periods indicated the necessity of considering different nuclear reactions. The method utilized to clarify the various possibilities is dependent upon the chemical identification of the active elements.

A. Problems involved in the studies of artificial disintegration

A few preliminary remarks relative to the research methods and problems involved in a radioactivity study of this nature should be made. Three main problems must be kept in mind by the investigator.

First, there is a question of measurement. The detection and identification of the various active substances depends upon the determination of the magnitude and the type of radioactivity. This phase of the investigation also involves the chemistry necessary to purify the starting materials and the separations essential to prove that new atomic species have been produced.

Second, the effect of naturally radioactive substances which might be present in the materials under examination must be remembered.

Third, with uranium, the possibility of transuranium elements being formed looms as an important factor. Should such be the case, numerous questions come to mind, most of which can be summarized in one question, "What would be the chemical behavior of these elements?" The chemical properties which might be associated with these elements have been mentioned previously.

With respect to the first of these problems, it must be remembered that in all cases of artificial radioactivity, minute unweighable amounts of substances are being utilized. They can be detected only by the ionization which their radiations produce. To be sure, this must not be considered as an uncertainty in the proof of their existence. For example, there is no longer any question of the existence of the naturally active elements even though, in nearly all cases, their presence likewise is demonstrated only through the effect of their radiations.

Up to the present time artificially radioactive elements have been obtained in even smaller amounts than some of the naturally active elements, hence it would seem that circumstances will be extremely unfavorable for their separation and identification. However, to discuss a nuclear reaction satisfactorily, it is essential that the active elements involved be separated chemically. Such an analysis consists of adding to the irradiated material small amounts of elements as carriers which are either isotopic or very closely related chemically to the material being examined, and effecting a separation of the various constituents. The activity of the various fractions obtained can then be determined, and the active substance identified. The principle involved is that of the radioactive indicator method, which has been widely used in the past to observe the course of different chemical and physical processes. In this instance, however, the carriers are added to assist in separating the active constituents, instead of adding a radioactive material as an indicator for more common elements.

In the case of the artificially produced radioactive elements, it is also possible to add to the irradiated material (carefully freed of ordinary active materials previous to irradiation) an amount of an ordinary beta-active element. Then if the induced activity and the added activity (recognizable by its characteristic period) can be resolved by chemical means, it can be assumed that the two activities are not due to isotopes.

Direct applications of this principle will be illustrated during the discussion of the chemical separations involved in the study on uranium.

The methods of identification make use of the usual devices for observing radioactivity. Naturally they must be very sensitive, since the amounts of the materials and, frequently, the intensity of the radiations are very low. Geiger-Müller counters which register the number of radiation particles penetrating the tube per minute have been extensively used. For making direct conclusions concerning the nature and the speed of the emitted particles, the Wilson cloud chamber is extremely practical. To absorb certain of the radiations, screens have been used. The sensitive Hoffman type and Wulff type electrometers are extensively employed in different laboratories where this problem is being investigated.

Regardless of whether the material decomposing is a naturally occurring or an artificially produced element, the radioactive disintegration for a homogeneous substance always follows a simple exponential law. That is, in a given unit of time the same percentage of the atoms present will always decompose. Therefore, when the intensity of the activity is plotted logarithmically against the time, the "decay curve" obtained will be a straight line for a homogeneous substance.

For many elements the decay curves are simple exponentials. For others, however, they must be analyzed into two or more exponentials. Such is the case for uranium which has been activated. For two substances, each of which is decomposing at its own specific rate, the "decay curve" is the resultant of the two straight-line exponential curves for each of the two substances. For example, in the case of a mixture of two substances one of which has a very short half-life and is disintegrating to form the second, which has a very long half-life, the decay curve initially shows a very rapid decrease of activity with respect to the time, but eventually changes into a straight-line exponential curve which is characteristic for the longer-lived substance. By subtracting the value for the longer-lived substance it is possible to determine the value for the material with the short half-life, the resulting curve also being a straight line. Conversely, if a substance of a long half-life disintegrates into a very short-lived element, after attaining "radioactive equilibrium," only a straight line is obtained. In this case the presence of the short-lived substance can be established only through chemical separations followed by activity measurements.

In case there are more than two active substances present, the situation is even more complicated. The various processes of disintegration taking place must then be determined by pursuing measurements for longer periods of time, by making chemical separations, and, in the case of induced radioactivity, by varying the period of bombardment in order to change the relative quantities of the various materials which are being rendered active. In the case of uranium these last points are very important.

Referring back to the second problem previously mentioned, the effect of naturally active elements must be anticipated when observing the activated uranium. The naturally active substances might possibly interfere with the chemical separations necessary to prove the presence of elements possessing the induced activity. Their presence might also interfere with the determination of half-life periods and the estimations of the gamma radiations of the artificially produced atoms. On the other hand, the presence of naturally active substances might provide a radioactive indicator which would be useful in following the chemical separations.

A résumé of the three known radioactive series is given in table 11 and figure 1. Interesting facts are the following:

(*1*) UI and UII are isotopes. Both have exceptionally long half-life periods and are alpha-emitting. They will, therefore, not interfere with the detection of substances of relatively short half-life periods involving a matter of minutes, days, or weeks. Should an isotope of one of these forms be produced no difficulty will arise. When radioactive equilibrium for the above has been established, the quantity of UII is found to be very small.

(*2*) Dempster (22, 23, 24) has recently reported the amount of a third

TABLE 11

Half-life periods and radiations of the chief disintegration series

URANIUM RADIUM SERIES	T*	RADIATION	ACTINIUM SERIES	T	RADIATION	THORIUM SERIES	T	RADIATION
Uranium	4.4 × 10^9 yr.	α	Actino-uranium	ca. 4 × 10^8 yr.	α			
Uranium X_1	24.5 days	β	Uranium Y	24.6 hr.	β	Thorium	ca. 1.8 × 10^{12} yr.	α
Uranium X_2	1.14 min.	β, γ	Protoactinium	3.2 × 10^4 yr.	α	Mesothorium 1	6.7 yr.	(β)
Uranium Z	6.7 hr.	β						
Uranium II	3 × 10^5 yr.	α	Actinium	13.5 yr.	(β)	Mesothorium 2	6.13 hr.	β, γ
Ionium	8.3 × 10^4 yr.	α	Radioactinium	18.9 days	α	Radiothorium	1.9 yr.	α
Radium	1590 yr.	α	Actinium X	11.2 days	α	Thorium X	3.64 days	α
Radon	3.82 days	α	Actinon	3.92 sec.	α	Thoron	54.5 sec.	α
Radium A	3.05 min.	α	Actinium A	0.002 sec.	α	Thorium A	0.14 sec.	α
Radium B	26.8 min.	β, γ	Actinium B	36 min.	β, γ	Thorium B	10.6 hr.	β, γ
Radium C	19.7 min.	α, β, γ	Actinium C	2.16 min.	α, β	Thorium C	60.5 min.	α, β
Radium C″	1.32 min.	β	Actinium C″	4.76 min.	β, γ	Thorium C″	3.1 min.	β, γ
Radium C′	ca. 10^{-6} sec.	α	Actinium C′	0.005 sec.	α	Thorium C′	10^{-9} sec.	α
Radium D	22 yr.	β	Actinium D (lead)			Thorium D (lead)		
Radium E	5.0 days	β						
Radium F (polonium)	140 days	α						
Radium G (lead)								

* T = half-value period.

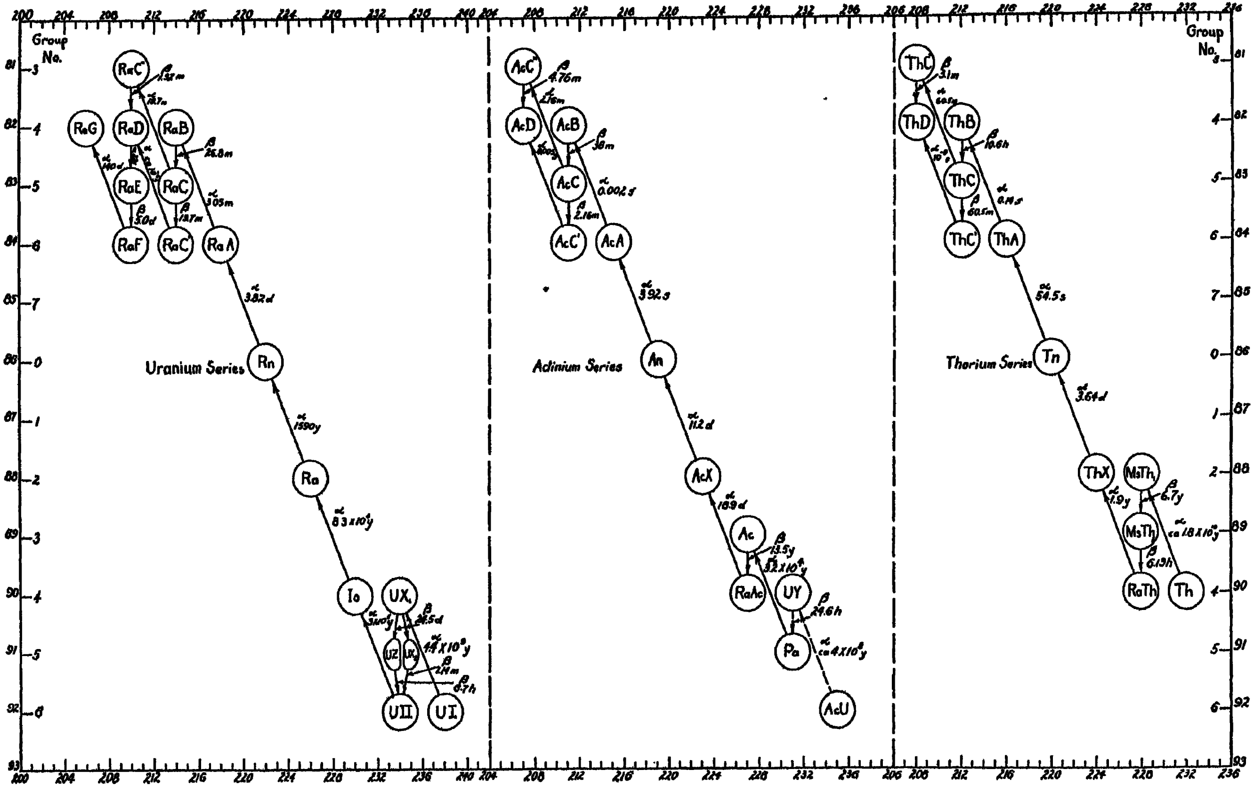


FIG. 1. The three natural radioactive series in an atomic number–atomic weight scheme. In α-emission the element is shifted four places to the left and two upward; in β-emission the element is shifted one place downward.

uranium isotope of atomic mass 235. Hence it is essential that this atomic species be considered in setting up the nuclear reactions taking place. The relative abundance of the three known uranium isotopes (UI^{238}, UII^{234}, U^{235}) is 1:0.007:0.00006.

(*3*) More troublesome are the three beta-emitting isotopes UX_1, UX_2, and UZ. UX_1 is an isotope of thorium ($Z = 90$; half-life = 24.5 days). UX_2 (68.4 sec.) and UZ (6.7 hr.) are both isotopes of protoactinium (No. 91). Unless these elements are removed, it will be found that their activity with respect to that of the artificially produced substances will be very appreciable. Even though they are removed before the start of an experiment, it must be remembered that within a few hours their concentration will again be relatively high compared to the artificially produced elements. Likewise, these elements are being formed constantly even during the bombardment of uranium. Hence if the irradiation is carried on for several hours, as is necessary to prove certain of the changes which are occurring, a considerable excess of UX and a very appreciable amount of UZ with respect to the activated materials may result during the bombardment period.

(*4*) Often, members of both the thorium and actinium series may have been present in the original source of the uranium salts. This implies that a careful purification of the uranium must be made.

With reference to the third question as to whether or not the transuranium elements might be formed, the following questions must be asked: (*a*) Should these elements be formed, can they be easily separated from uranium? (*b*) Should they be easily separated from the uranium, can they be separated without difficulty from one another? (*c*) Should they exhibit very short half-life periods, can chemical separations be performed rapidly enough to be of aid in establishing the exact nature of the disintegration series? (*d*) Should more than one transuranium element be formed, are they produced under identical conditions? In other words, will bombardment with slow and fast neutrons be of assistance in determining the disintegration processes? (*e*) Should elements of very long half-life periods, and in particular alpha-emitting elements, be formed, will it be possible to detect and identify them? (*f*) Would deuteron bombardment supplementary to the neutron bombardment be of assistance in identifying the nuclear reactions? (*g*) Since *K*-electron capture has been observed as taking place in the heavier elements in contrast to the emission of positrons, would such occur with uranium? (*h*) Is it possible that perhaps alpha particles, or other forms of radiations, are emitted only during the time of bombardment? Should such a change take place, the nature of the nuclear reactions noted after cessation of bombardment would probably be drastically different than if no special types of reactions are occurring only during the bombarding period.

B. The experimental results on bombarded uranium

With these questions in mind, a discussion of the work of Fermi, of Hahn, Meitner, and Strassman, of Curie and Savitch, and of others will be reviewed.

The initial report on the induced radioactivity of uranium was made by Fermi (8, 31) in 1934. Half-life periods of 10 sec., 40 sec., 13 min., and at least two other periods varying from 40 min. to 1 day were mentioned. It was stated that electrons had been detected and that Geiger-Müller counters were used to note the radiations.

Fermi (31, 20) and his associates, Amaldi, D'Agostino, Rasetti, and Segrè, cited evidence that the substance with the 13-min. half-life period could easily be separated from most of the heavy elements, and that it was not isotopic with uranium. The concentrated uranium nitrate solution used for the irradiation process was diluted with 50 per cent nitric acid. A small amount of a manganese salt was added and the manganese precipitated as the dioxide from a boiling solution upon addition of sodium chlorate. It was found that the manganese dioxide carried a large percentage of the material possessing the 13-min. half-life period. This indicated that the element with this characteristic was not isotopic with uranium. It is obvious why this particular reaction was chosen for the first determinations. Since the activity was due to a beta-particle emission, according to the Fajans–Soddy rule, an element of higher atomic number than 92 would be indicated. This assumes no alpha-particle emission. A higher congener of manganese and rhenium would thus be expected. The chemistry of manganese might possibly be adaptable, even though there would probably be a considerable difference in the chemical properties of manganese and ekarhenium. A review of the chemistry of rhenium, which should be more closely allied to an element 93, shows that this particular separation is by no means the best, even though for the original exploratory work it served a definite purpose.

Having proved that the 13-min. active substance was not isotopic with uranium, Fermi *et al.* (31) tested the possibility of isotopes of elements 90 (thorium) and 91 (protoactinium). The very short half-life period of UX_2 (68.4 sec.), an isotope of protoactinium, rendered this phase of the work more difficult. The irradiated uranium nitrate solution was mixed with some UX_1 and UX_2, whose activities produced about 2000 impulses per minute on the Geiger counters. Lanthanum and cerium were added to act as carriers for the UX in the chemical separations. The precipitation of manganese dioxide was carried out, using the chlorate oxidation in nitric acid solution. It was found that the precipitated manganese dioxide again carried only the 13-min. substance. No trace of UX_1 (24.5 days) was found in the precipitate. Likewise none of the UX_2 was noted, even though the measurements of the activity were made within 2 min. after the manganese dioxide was precipitated.

The elimination of elements 88 (radium) and 89 (actinium) as the source of the activity was shown by adding $MsTh_1$ as a natural radioactive indicator, with barium and lanthanum as carriers, to the irradiated uranyl nitrate solution. The results were negative.

The Italian investigators likewise added inactive lead and bismuth to the irradiated uranium. The conditions for precipitating the manganese dioxide were then regulated so that the manganese could be precipitated without inclusion of either the lead or the bismuth. In each case the 13-min. active material precipitated with the manganese.

These experiments indicated the possibility that the substance possessing the 13-min. half-life period was not an isotope of uranium (92), protoactinium (91), thorium (90), actinium (89), radium (88), bismuth (83), or lead (82). Its chemical behavior excluded ekacesium (87) and emanation (86) from consideration.

Fermi and his associates (10) reasoned that the lack of positive evidence of a relationship of the 13-min. substance with any of the heavier elements indicated the possibility of an element of atomic number greater than 92. Further they suggested that if element 93 were formed, chemically it should be congener of manganese and rhenium, a hypothesis which they proved by showing that the 13-min. material coprecipitated with rhenium sulfide in hydrochloric acid solution. At first they ruled this evidence as being weak, since several elements can be precipitated with hydrogen sulfide under about these same conditions. The later splendid work of Hahn, Meitner, and Strassmann substantiated their conclusions, however.

Fermi and his associates (31) mentioned that the possibility of similar chemical properties for elements 93, 94, and 95 would render it very difficult to distinguish between these elements. (Reference to an earlier part of this paper will give more detailed information about the close relationship of these elements.)

In a later paper Fermi and his coworkers (34) announced the detection of an active substance of about a 90-min. half-life. They wrote, "A more effective reaction for obtaining the 13-minute active product is the following: irradiated uranium nitrate is dissolved in diluted hydrochloric acid; some rhenium nitrate is added, and then rhenium is precipitated as sulphide by addition of sodium thiosulphate. This precipitate carries about 50% of the activity; and sometimes more. The percentage of UX_1 and of UX_2

found in the rhenium precipitate varies also with the conditions of the reaction (particularly with the acidity), but can be made very low, probably less than 1%. It was actually possible to separate the 13-minute active product and to measure its period using uranium which had not been purified at all from UX. The 90-minute active product has apparently chemical properties very analogous to those of the 13-minute active product as in every type of reaction they are always obtained in about the same percentage. These activities seem, therefore, both to be due to products with atomic number higher than 92, and possibly to isotopes of a same element."

Von Grosse and Agruss (75, 76, 77, 78), on the basis of certain experiments on protoactinium, criticized Fermi's contention that the 13-min. active material was an element 93, and that the 90-min. material was material isotopic with the 13-min. substance. Their thought was that one should expect, according to the periodic law, different properties for the highest homolog of manganese from those assumed by Fermi. Accordingly von Grosse and Agruss (78) performed experiments using protoactinium as a radioactive indicator. In one test they precipitated the manganese from a solution containing uranyl nitrate, nitric acid, protoactinium, and manganese nitrate by the addition of sodium chlorate. The activity in the uranyl nitrate filtrate was precipitated with zirconium phosphate. The activities of both the manganese oxide precipitate and of the material recovered from the uranyl nitrate filtrate were determined. In a second experiment potassium perrhenate in a hydrochloric acid solution was mixed with a definite amount of protoactinium. The rhenium was precipitated as the sulfide, using sodium thiosulfate. After boiling the solution, the rhenium sulfide was filtered off, impregnated with zirconium oxychloride, fumed with sulfuric acid, and ignited, and then its alpha-activity was measured. The protoactinium in the filtrate was recovered with zirconium phosphate as in the first experiment. Table 12 shows the results of this investigation, which did not include any irradiated uranium as one of the materials to be treated. These results seem identical within experimental error. Von Grosse and Agruss suggested that Fermi's 13-min. active material would also show the characteristic reaction of element 91, namely the precipitation, together with zirconium, of the 13-min. substance by phosphoric acid from a strongly acid solution (20 to 30 per cent hydrochloric acid or nitric acid solution). They felt that Fermi's experiments with UX_2 were inconclusive, because the very short life of that radioactive material introduced very great difficulties in the chemical separations. They also hinted that the 13-min. material be named radiobrevium, which is an isotope of protoactinium.

Von Grosse and Agruss (76), however, withdrew their objections to

Fermi's conclusions, after Fermi announced that the zirconium phosphate precipitate produced according to the conditions outlined by von Grosse did not contain any of the 13-min. activity. The work of Hahn, Meitner, and Strassmann also emphasized the correctness of Fermi's conclusion.

I. Noddack (67) also criticized Fermi's original reports, on the basis that Fermi had not investigated whether or not elements other than protoactinium, thorium, actinium, radium, bismuth, and lead as well as emanation and ekacesium might possibly be responsible for the half-life periods and the chemical reactions which Fermi claimed for element 93. Accordingly she performed experiments using manganese nitrate in a nitric acid solution, to which she added small amounts of a large number of different elements, either in the form of soluble salts or as colloids. The resulting mixture was boiled and treated with potassium chlorate. The manganese dioxide precipitate contained titanium, columbium, tantalum, tungsten, iridium, platinum, gold, and silicon in practically quantitative amounts. Antimony, lead, bismuth, nickel, and cobalt were partly precipitated. She also precipitated manganese dioxide from a solution containing some polonium, finding that the polonium precipitated almost quantitatively with the manganese. Fermi did not attempt to prove that polonium was absent. I. Noddack also commented on the well-known fact that rhenium sulfide, like many other sulfides, can adsorb ions and hence might carry down the artificially radioactive substances during the precipitation. Her objections were explained later by Fermi as well as by Hahn, Meitner, and Strassmann.

TABLE 12

Results of an experiment using protoactinium as a radioactive indicator

	REACTION	
	Precipitation of manganese dioxide with sodium chlorate	Precipitation of rhenium sulfide with sodium thiosulfate
Behavior of element 91	99 to 100 per cent precipitated in hot 30 per cent nitric acid	40 to 60 per cent precipitated in hot 15 per cent hydrochloric acid
Behavior of Fermi's element 93	Large per cent of activity precipitated in hot concentrated nitric acid	About 50 per cent of activity precipitated in hot concentrated hydrochloric acid

The work of Hahn and Meitner (39 to 49, 59 to 63) has done much to clarify the position of elements 93 and 94. The initial step in the chemistry which they performed is important in the chemical separations made later in their analyses. Protoactinium, thorium, and uranium were found to be quantitatively precipitated by sodium hydroxide. The salts of the other elements of higher atomic number, as well as those of ekarhenium, should be soluble. Therefore, they added potassium perrhenate and platinum chloride to the irradiated UX-free uranium solution before the addition of sodium hydroxide. The mixture was filtered to remove uranium and any protoactinium which might be present. The filtrate, which had been made slightly acid, was treated with hydrogen sulfide. The precipitated platinum sulfide was removed by filtration. The resulting filtrate was then treated with an equal volume of 37 per cent hydrochloric acid, and the rhenium sulfide precipitated by further addition of hydrogen sulfide. They found that both the 13-min. and the 90-min. active substances were precipitated with the platinum, and that the rhenium sulfide was inactive. If only the rhenium were added, then both active materials went with the rhenium sulfide, although in smaller amounts. They also showed that if UZ (No. 91) were added, no precipitation of this element took place with the sulfide, hence disproving the contention of von Grosse and Agruss (75) that the active materials were isotopes of protoactinium. The fact that the 13-min. and the 90-min. materials precipitated most readily under the conditions for precipitating the platinum sulfide indicated that these substances were probably more like the platinum group metals than like rhenium and probably belonged to elements beyond element 93.

Hahn and Meitner (43) were particularly careful to prove the exclusion of element 91 (protoactinium). To irradiated UX-free sodium uranate dissolved in dilute hydrochloric acid they added about 10 mg. of platinum and rhenium, 5 mg. of zirconium, and some UZ. The amount of UZ (β-emitting, 6.7 hr.) corresponded in its intensity to about an equivalent of the amount of UZ in 150 g. of uranium. A sodium hydroxide precipitation was carried out, the resulting precipitate and filtrate being treated separately. The filtrate, after being made slightly acid, was saturated with hydrogen sulfide. It was noted that the 13-min. and the 90-min. substances concentrated with the platinum sulfide in a yield of about 30 to 34 per cent. The precipitate from the hydroxide containing the uranium was dissolved in 25 per cent hydrochloric acid, and an additional 5 mg. of zirconium added. The UZ was precipitated with the zirconium phosphate. A portion of this precipitate was measured in the electroscope, and the remainder with a counter. The agreement obtained between the treatment with the zirconium phosphate and the platinum sulfide precipitation showed that the 13-min. and the 90-min. substances certainly contained less than 1/1000 of the amount of the UZ originally added as an indicator. This showed in a very direct manner that both of these materials were not isotopic with element 91, as had been suggested by von Grosse.

As Hahn and Meitner (44) continued their investigations of the exact nature of the disintegrations taking place in the bombarded material, it was observed that the half-life value of 90 min. was probably in error and should be regarded as 100 min., even though there was a qualification that perhaps this activity was due to two substances, one of a shorter half-life than 100 min. and the other perhaps of about 2 to 3 days. Subsequently it was determined that the 100-min. activity was due to a mixture of a 59-min. and a 66-hr. substance. Later Hahn, Meitner, and Strassmann (47) reported evidence for the existence of a substance with a half-life of about 12 hr., whose properties indicated that it was a platinum group homolog.

At this same time the German investigators (47) reported a characteristic distinction between the platinum homologs and ekarhenium, based on the behavior of these materials toward metallic platinum or platinum saturated with hydrogen. Experiments were conducted on unbombarded uranium in equilibrium with its decomposition products. It was shown that only a very slight amount of UX_1 (thorium isotope) was adsorbed on platinum immersed in a hot solution of the uranium salt in a normal hydrochloric acid solution. For a short period of time the amount adsorbed was negligible. When similar experiments were tried with the transuranium elements it was noted that the ekarhenium did not separate, whereas the homologs of the platinum group did plate out in considerable amounts. The results with polished platinum foil were the same as with hydrogen-saturated platinum. The amount of adsorption was apparently not affected if weighable amounts of lead, thallium, and bismuth were added to the solution.

In 1935 Fermi, Amaldi, D'Agostino, Pontecorvo, Rasetti, and Segrè (7) presented their results on the slowing down of neutrons by paraffin and other substances rich in hydrogen. Slow neutrons are produced when neutrons are forced to pass through layers of paraffin or water previous to their action on other substances. Generally, with slow neutron bombardment, the neutron is captured by the elements being bombarded, whereas with fast neutrons there may also be the emission of neutrons from the bombarded substance. (These particular reactions will be considered specifically later in this report.)

The Italian investigators observed that of the four periods previously reported (15 sec., 40 sec., 13 min., and 100 min.) the 40-sec. period was not affected by the use of both slow and fast neutrons, whereas there was a very appreciable increase in the intensities of the 15-sec., the 13-min., and the 100-min. activities. The increase of intensity was found to be 1.6. They suggested that the value for the 15-sec. ratio is perhaps not exceptionally accurate. Since the three periods mentioned were all about equally water-sensitive, the conclusion was that they were all probably due to the same primary process, whereas the 40-sec. activity was due to an independent primary process.

The fact that the intensity of the activity due to the three periods was changed about equally for all, suggested that the three activities were perhaps due to a chain process of disintegration or to a complicated branching phenomenon. A certain amount of evidence was obtained by Fermi (7) and his coworkers for the existence of the chain process from the decay curves obtained when a thick layer of irradiated uranium was measured on the electrometer. These exponential curves showed that the initial activities of the 13-min. and the 100-min. periods were about in the ratio of 100:45, the half-value thickness for the beta rays of the 13-min. activity is 0.14 g. per cm.^{2} of aluminum; for the longer period the ratio was not definitely determined with any accuracy, but it was decidedly less than the former value and probably about one-half. This indicated that the number of disintegrations for the 13-min. and the 100-min. substances are about equal, which is consistent with the assumption that they are connected by a chain process.

At this same time, the Italian investigators (7) reported their experiments relative to the criticisms made by von Grosse and Agruss. Precipitation of the active materials with various sulfides was made. Silver, copper, lead, and mercury salts were used. The acidity of the different solutions was varied. The amount of activity in the precipitated sulfides was generally good. The sulfide reaction appeared successful, even in the presence of a hydrofluoric acid solution of tantalum. They also proved that the activity was not due to a protoactinium isotope, by dissolving specially purified and irradiated uranium oxide in a 25 per cent hydrochloric acid solution to which were finally added solutions of zirconium nitrate and phosphoric acid. The precipitated zirconium phosphate was inactive, whereas the sulfide precipitate obtained by treatment of the filtrate with hydrogen sulfide was active. This reaction proved the nonidentity of the active material with a protoactinium isotope. This conclusion was also reached by Hahn and Meitner, as indicated above.

Fermi (7) likewise reported in this same paper the first evidence which he and his assistants obtained for some separation of the 13-min. and the 100-min. active materials. This was done by dissolving the carefully purified irradiated uranium oxide in hydrochloric acid, and pouring the resulting mixture into ammonium carbonate solution until the uranium precipitate was again completely dissolved. Lead nitrate or manganese nitrate was added to precipitate the carbonates, which were slightly active. The clear filtrate was treated with hydrogen sulfide in the presence of copper salts. The copper sulfide likewise carried a fraction of the activity. The ratio of the two activities, however, was different in the two precipitates, the 13-min. substance apparently being present in larger quantity in the sulfide precipitate, thereby indicating a partial separation. This same evidence suggests that the active elements must be transuranic in nature. At this time, Fermi assumed that the 15-sec., the 13-min., and the 100-min. activities are chain products, due probably to the elements with atomic numbers 92, 93, and 94, respectively.

Hahn, Meitner, and Strassmann (47) in repeating Fermi's experiments on the effect of slow and fast neutron bombardment did not obtain the same results. Accordingly they began a series of experiments to determine the effect of various periods of bombardment, using both slow and fast neutrons. The decay curves obtained showed systematic variations from one another, depending upon whether the time of bombardment was short (5 to 10 min.) or long (30 to 120 min.).

A short period of bombardment with fast neutrons gave in addition to the rapid decay during the first few minutes (due to the 10-sec. and the 40-sec. substances) an activity which corresponded closely to Fermi's 13-min. material. With slow neutrons the period of decay was decidedly longer. This indicated a relatively larger amount of the so-called 100-min. substance present in this instance. The curves for the irradiation with slow neutrons showed definitely that there were more transformation products than when bombardment was made with fast neutrons. After long periods of bombardment, the amounts of the longer lived substances naturally were greater. For these periods of long irradiation, the formation of UX from the uranium caused difficulty.

In their report Hahn, Meitner, and Strassmann (48) pointed out one very important factor relative to the chemistry involved in the separations of the transuranic elements. They were able to show conclusively, after precipitation with hydrogen sulfide from hot, strongly acid, hydrochloric acid solutions, that the naturally occurring radioelements down to 85, bismuth, remained entirely in the filtrate, whereas the transuranium elements precipitated under these conditions.

These investigators also made chemical separations on the carefully purified uranium which had been subjected to both rapid and slow neutrons for varying periods of irradiation. In these experiments it was likewise shown that systematic variations occurred in the decay curves, demonstrating that bombardment with slow neutrons intensified certain of the processes, and not others. Their conclusion at this time, contrary to the work of Fermi and his assistants, was that the 13-min. substance was formed only after bombardment with fast neutrons, whereas the 100-min. substance could be produced with both fast and slow neutrons, the yield of the latter being greater in the case of slow neutron bombardment.

Another observation made at this time was that apparently transformation products other than the transuranic elements were being created, suggesting therefore that elements 90 to 92 were the active constituents. Hence they proceeded to consider the nature of the nuclear reactions involved in the formation of the transuranium elements and the subsequent disintegration series.

This possibility of thorium, protoactinium, and uranium being present caused Hahn and Meitner (62) to assume that the following reactions were occurring:

$$U^{238} + n \rightarrow Th^{235} + \alpha$$

$$Th^{235} \rightarrow Pa^{235} \xrightarrow{\beta} U^{235} \xrightarrow{\beta} \text{Eka-Re} \rightarrow ?$$

The above reaction is one which might be expected upon neutron bombardment of uranium, provided the proper energy relationships existed at the time of bombardment.

The evidence cited by Hahn, Meitner, and Strassmann (47) for the existence of the thorium isotope was based on certain chemical separations. Several grams of UX-free uranium were bombarded for 10 to 15 min. with slow neutrons. The uranium was dissolved as rapidly as possible in 2 normal hydrochloric acid; two precipitations as the sulfide were made after the addition of 10 mg. of platinum, in order to eliminate the transuranium elements. After addition of ferric chloride to the filtrate, the uranium was precipitated with ammonia and dissolved in an excess of ammonium carbonate. The iron hydroxide contained the UX, the thorium isotope, and the protoactinium isotope. Fifteen minutes after cessation of bombardment, the measurement of the activity was begun. The decay curves showed a rapid decrease in intensity of radiation at first, but gradually changed to the characteristic curve for UX. The half-life of the substance causing the initial change in the curve was found to be 4 min. after subtraction of the value for the UX. The authors suggested that the methods of chemical separation used did not permit distinguishing between Th^{235} and Pa^{235}. They believed that this new activity must be associated with Th^{235} on the basis of the radioactive disintegration laws.

This value of 4 min. for a thorium-235 did not agree with other values for the disintegration of either thorium or protoactinium. There is an active thorium isotope (233) of a half-life of 25 min. and a protoactinium of 233 with a short half-life of about 2.5 min., as reported by I. Curie *et al.*

In a later report Hahn, Meitner, and Strassmann (48) clarify the question about this thorium isotope, which they unfortunately postulated. They noted, in some of their experiments, that the substance with the 23-min. activity was scattered through precipitates other than those containing the uranium. For example, in the zirconium phosphate precipitation used for proving the presence of thorium isotopes, some of this active substance was found to be present. Subsequently these observations were explained as follows: Apparently during the bombardment of the uranium material a sort of Szilard–Chalmers (73) separation occurred, in that a portion of the uranium isotope was present in other than the hexavalent condition. By heating the bombarded uranium with nitric acid, the tetravalent uranium was reconverted to the hexavalent state. The zirconium phosphate precipitate, under these conditions, did not contain any of the short-lived material. Thus it was possible for the German investigators to eliminate the above nuclear reactions from consideration as one series in the disintegration of the transuranium elements.

C. The active transformation processes

Hahn, Meitner, and Strassman (48, 60, 62, 63) have suggested the following three series of reactions to show the genetic relationship of the different substances obtained when uranium is bombarded with neutrons. No suggestion of atomic mass values was considered.

$$\mathrm{U} + n \rightarrow {}^{10\,\mathrm{sec.}}_{92}\mathrm{U} \xrightarrow{\beta} {}^{2.2\,\mathrm{min.}}_{93}\text{Eka-Re} \xrightarrow{\beta} {}^{59\,\mathrm{min.}}_{94}\text{Eka-Os} \xrightarrow{\beta} {}^{66\,\mathrm{hr.}}_{95}\text{Eka-Ir} \xrightarrow{\beta}$$

$${}^{2.5\,\mathrm{hr.}}_{96}\text{Eka-Pt} \xrightarrow{\beta} {}_{97}\text{Eka-Au} \rightarrow ? \qquad \text{(I)}$$

$$\mathrm{U} + n \rightarrow {}^{40\,\mathrm{sec.}}_{92}\mathrm{U} \xrightarrow{\beta} {}^{16\,\mathrm{min.}}_{93}\text{Eka-Re} \xrightarrow{\beta} {}^{5.7\,\mathrm{hr.}}_{94}\text{Eka-Os} \xrightarrow{\beta} {}_{95}\text{Eka-Ir} \rightarrow ? \qquad \text{(II)}$$

$$\mathrm{U} + n \rightarrow {}^{23\,\mathrm{min.}}_{92}\mathrm{U} \xrightarrow{\beta} {}_{93}\text{Eka-Re} \rightarrow ? \qquad \text{(III)}$$

1. The chemical identification of uranium isotopes

From the above three transformation series it is seen that active uranium isotopes were formed by irradiation with neutrons.

The evidence for these isotopes may be shown by following one of these materials (the 23-min. substance) through the chemical separations. (The exact conditions for exciting uranium to form this active isotope will be mentioned later.) A UX-free preparation, bombarded with slow neutrons under the proper conditions and then dissolved in a 2 *N* hydrochloric acid solution, was saturated with hydrogen sulfide. The filtrate, containing the uranium, was then treated with a large excess of sodium acetate and the sodium uranyl acetate precipitated with concentrated acetic acid. The activity of the uranyl acetate precipitate was found to decrease during the first 1.5 to 2 hr., and then to increase on account of the gradual formation of UX from the uranium. The decrease showed the presence of a homogeneous substance with a half-life period of 23 min. That the activity of the uranyl acetate might be due to the possible adsorption of the 23-min. substance was guarded against by making fractional precipitations of the acetate on a large amount of irradiated uranium. Three precipitations were made, stepwise, from the uranium solution. Equal quantities of the first and third fractions were tested for their content of the 23-min. substance. The amount of activity was exactly the same for every unit weight of uranium. The possibility of adsorption was eliminated by this procedure, which also showed that this material was chemically identical with uranium. Such a treatment naturally implies that the bombarded uranium had been treated with nitric acid to eliminate any possibility of a Szilard–Chalmers (73) separation.

Since the 23-min. material emits beta particles, it must form an ekarhenium. No definite evidence has been obtained, up to the present, for this particular ekarhenium. Should it be a stable ekarhenium its existence would be very difficult to prove. Also, on the other hand, should this isotope of ekarhenium possess a very long half-life, its presence would not be easily determined.

The existence of the 40-sec. uranium isotope may be proven in similar fashion, according to the German investigators. In this instance fast neutrons are used to produce the active element. The 23-min. material is not formed under these conditions. The purified uranium was bombarded for a very short period, and the uranyl acetate precipitate produced as rapidly as possible. The investigators reported that they were able to begin the radioactive measurements in about 2.4 min. after cessation of bombardment. The initial decline of the decay curves was much more rapid than in the case of the 23-min. material.

Thus far, no chemical test has been successfully made of the 10-sec. substance formed during a 15-sec. bombardment of uranium.

2. The distinction of ekarhenium from homologs of the platinum metals

One difference between ekarhenium and the homologs of the platinum metals is based on the behavior of these elements with respect to the noble metals. The ekarhenium isotopes will not precipitate on platinum foil during electrochemical treatment, whereas the platinum homologs will. This distinction is very characteristic. A typical experiment, as carried out by Hahn, Meitner, and Strassmann (48), begins by bombarding some purified uranium for about 36 min. After this length of irradiation approximately three-fourths of the equilibrium amount of ekarhenium (16 min.) was formed in contrast to about one-fourth that of ekaosmium (59 min.). The uranate was dissolved in 2 *N* hydrochloric acid, which was then diluted to 1 normal acid concentration. A piece of platinum foil, previously washed with hydrogen, was then immersed in the nearly boiling solution for about 10 min. After cleaning the foil with acid and water, the activity of the sheet was determined and found to be due only to precipitated ekaosmium. Control experiments were made, in which both the ekarhenium and ekaosmium were precipitated as the sulfide, the decay curves for these samples being much steeper at the outset, indicating that the percentage of ekarhenium was much greater than that of the ekaosmium.

The electrochemical separation of ekarhenium and the artificially produced noble metals is even more convincing when it is remembered that, on account of the very short life of the ekarhenium, it is necessary for the ekarhenium activity to be at least four times as intense in order to equal that of the ekaosmium.

These particular experiments are likewise excellent evidence of the very noble character of the homologs of platinum metals.

3. The precipitation of the homologs of the platinum metals and the non-precipitation of ekarhenium with metallic bismuth

In another series of experiments the German investigators found that it was possible to precipitate the artificially produced noble metals along with metallic bismuth from a bismuth salt solution, using alkaline stannous chloride as the reducing agent.

UX-free uranium was irradiated in the form of ammonium pyrouranate with neutrons for about 60 min. From a warm solution of the uranate in approximately 5 per cent hydrochloric acid, about 30 mg. of bismuth was precipitated with hydrogen sulfide. The bismuth sulfide which contained the precipitated transuranic elements—mainly ekarhenium (16 min.) and ekaosmium (59 min.)—was dissolved in 25 per cent hydrochloric acid with the addition of a few drops of nitric acid. The nitric acid was used to guarantee complete solution of the platinum homologs. The clear filtrate, after dilution with water, was almost neutralized with sodium hydroxide, mixed with alkaline stannous chloride, and warmed. Metallic bismuth precipitated carrying with it the platinum homologs, of which essentially only ekaosmium was present. The filtrate from the bismuth precipitation was poured into 25 per cent hydrochloric acid solution which contained some rhenium, and an equal volume of 35 per cent hydrochloric acid was added. The rhenium was then precipitated as the sulfide. The tin remained in solution, the ekarhenium going with the rhenium sulfide precipitate.

The decay curves (figure 2) show very clearly this particular separation. Curve A shows the decrease of activity of the metallic bismuth and the included platinum homologs. Curve B is much steeper, at the outset showing only the characteristic decay of ekarhenium (16 min.). Curve A is flatter, and shows the decomposition of the ekaosmium (59 min.). The bending of the curve for the ekarhenium (curve B) is explained as due to the formation of the second ekaosmium isotope (5.7 hr.) from the 16-min. ekarhenium. (This point will be mentioned again later.)

4. The precipitation of ekarhenium with nitron

One of the most typical precipitation reactions of rhenium is the nitron test (38). Rhenium, like nitrates, forms a very insoluble precipitate in a weak acetic acid solution with nitron. It was natural to think that perhaps ekarhenium would do likewise. A uranium preparation was bombarded for a short period in order to give a maximum amount of the 16-min. ekarhenium. This was dissolved in 20 per cent hydrochloric acid, mixed with some rhenium in the heptavalent form, and treated with hydrogen sulfide in the cold. Re_2S_7 separated. This precipitate was then dissolved in a warm solution containing sodium hydroxide and hydrogen

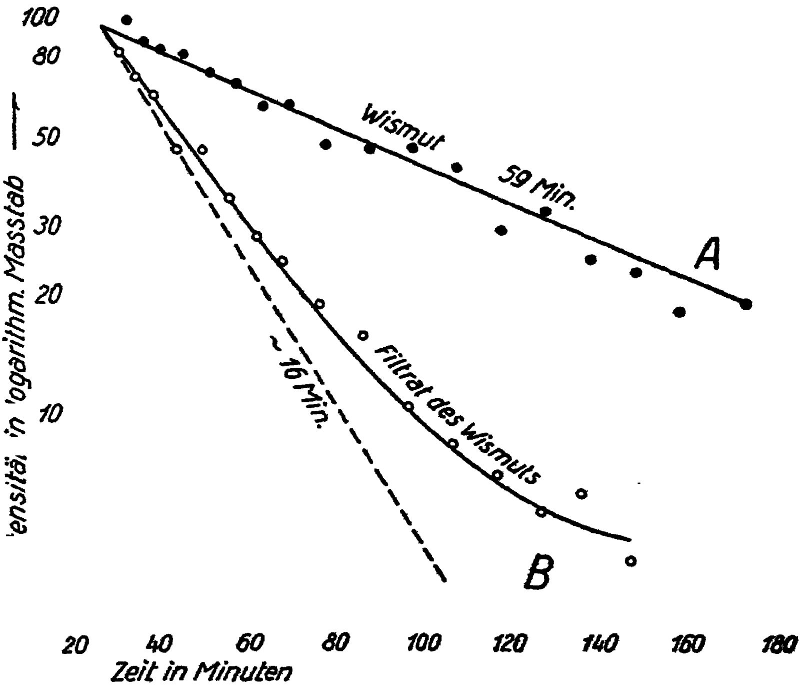


FIG. 2. The separation of ekarhenium from ekaosmium using metallic bismuth as the carrier for the ekaosmium (according to Hahn, Meitner, and Strassmann (48)).

peroxide. The resulting solution was acidified with acetic acid, cooled, and treated with nitron acetate. A voluminous precipitate of nitron perrhenate formed, which was found to contain a large quantity of the substance with the 16-min. half-life, along with a small amount of the 59-min. substance. Dissolving the precipitate in warm hydrochloric acid, almost neutralizing with sodium hydroxide, and adding a further quantity of nitron acetate gave a purer nitron perrhenate containing the 16-min. material in smaller amount but greater purity.

5. The use of sodium hydroxide to separate ekarhenium from the platinum homologs

Hahn, Meitner, and Strassmann (48) also observed the effects of sodium hydroxide upon hot solutions containing weighable amounts of sodium perrhenate, platinum chloride, and osmium ammonium chloride in the irradiated uranium preparations. Rhenium was found to remain quantitatively in solution, platinum was partially adsorbed, and the osmium was completely precipitated. The natural transformation products of uranium were quantitatively precipitated.

Hence an irradiated uranium, bombarded for a short period to give a large amount of the 16-min. isotope of ekarhenium and a small amount of ekaosmium, was treated with a small amount of sodium perrhenate and sodium hydroxide. Part of the ekarhenium went into the alkaline filtrate. The ekaosmium remained completely in the precipitate. Unfortunately part of the ekarhenium was adsorbed by the large quantity of uranium present. The decay curves of the filtrate and the precipitate showed the separation of the ekarhenium and the ekaosmium, as well as the formation of ekaosmium from ekarhenium.

The investigators succeeded in showing, with uranium that had been strongly bombarded and rapidly separated, that some of the 2.2-min. ekarhenium was separated with the 16-min. isotope. It was again noted that the 16-min. material disintegrated into the ekaosmium of 5.7-hr. half-life. Using uranium preparations bombarded for very long periods of time (those in which there was formed a larger concentration of elements 95 and 96), only a fraction of the ekairidium (No. 95) and the ekaplatinum (No. 96) was found in the filtrate.

6. The difference in volatility of the ekarhenium and the ekaosmium isotopes

As mentioned above (page 108), one would expect that ekaosmium should be volatile in the form of certain of its compounds, and that the chloride of ekarhenium should be more volatile than the chloride of ekaosmium.

The experiments of Hahn, Meitner, and Strassmann have shown this to be true.

Irradiated uranium was treated to precipitate the sulfides of ekarhenium and ekaosmium, with platinum as a carrier. Then a series of differentiated ignitions was carried out. For those experiments in which the ekaosmium would be expected to form an oxide, there was a decrease in the activity of the residue remaining after heating. The decay curves for this residue indicated an excess of ekarhenium. In other experiments in which the precipitated sulfides were treated with aqua regia, so that chlorine was present, evaporation to dryness and subsequent ignition showed a change in activity of the residue such that the residue was shown to consist of ekaosmium.

One such experiment consisted in collecting the sublimate and then comparing the activities of the volatile and non-volatile portions. The technique consisted in placing the crucible containing the platinum–osmium precipitate (which had been evaporated down with aqua regia) in a thick asbestos disk so that the bottom of the crucible could be strongly heated without the upper portion of the crucible walls becoming too hot. The crucible was covered with aluminum foil, which was cooled by placing a water-filled aluminum dish on top. The bottom of the crucible was gently heated, and the sublimate collected on the aluminum foil. A second piece of foil was then placed on the crucible, and the crucible was heated very strongly for a considerable period of time. The residue remaining after the ignitions was also measured for its activity. The results obtained were as follows: In the first sublimate the activity showed an excess of ekarhenium in the mixture. In the second sublimate the activity was weak, and was essentially only ekaosmium. (The activity half-life was about 60 min.) In the residue the activity was about ten times that of the second sublimate and was apparently due only to ekaosmium (T (observed) = 60 min.)

In other words, when the substances formed are the oxides or oxygen salts, the ekaosmium compound is the more volatile; if they are in the form of the chlorides, the ekarhenium compound is the more volatile, which is exactly as expected for the properties of these elements.

7. The differences in solubility of the sulfides of ekarhenium and ekaosmium in different concentrations of hydrochloric acid

According to the German investigators most of the transuranic elements are precipitated as the sulfides from a 2 N hydrochloric acid solution. With increasing acid concentration, the solubility of the ekarhenium sulfide increases. For example, from a 10 N hydrochloric acid solution a considerable portion of the ekaosmium precipitates, the ekarhenium being obtained by diluting the filtrate and saturating further with hydrogen sulfide.

8. Distinguishing the platinum homologs from one another

The experimental difficulties arising in the separations of the platinum group homologs are complicated, as one would expect. For example, a mixture might contain the two isotopes of element 94 (59 min. and 5.7 hr.), one of element 95 (66 hr.), and one of element 96 (2.5 hr.). The longer lived ekaosmium (No. 94) and the ekairidium (No. 95) are very weakly active. Hence for one set of separations, three different elements, as well as two isotopes of one of them, must be accounted for.

The differences between ekaosmium and ekairidium are such that certain of the reactions used to distinguish between ekarhenium and ekaosmium are applicable. For example, for these latter two elements (Nos. 93 and 94) several methods give indisputable evidence for the separation of the elements, according to Hahn, Meitner, and Strassmann. These are the precipitation of the osmium with metallic bismuth by the action of alkaline stannous chloride, the greater solubility of ekarhenium sulfide in concentrated hydrochloric solutions, and a partial precipitation of the ekaosmium with sodium hydroxide. These same reactions may be used to distinguish ekaosmium (No. 94) and ekairidium (No. 95). The chief factor in these separations is to continue bombardment for a sufficiently long period in order to build up the concentration of these elements of highest atomic number.

(A). The separation of ekaosmium and ekairidium

(*1*) *A partial separation using metallic bismuth as a carrier.* A partial separation of these two elements was found to occur when the bismuth salt solution containing the active material was treated with alkaline stannous chloride. (This treatment has been mentioned on page 128.) However, in this case, the uranium samples were irradiated for at least 10 hr. previous to the chemical separations.

The metallic bismuth precipitate was extremely active. The slope of curve A (figure 3) is steep at first, which is evidence for the short-lived ekaosmium (59 min.). The gradual bending of the curve shows the presence of an appreciable quantity of the 5.7-hr. ekaosmium. Ultimately curve A approaches the value of 66 hr., which is due to the ekairidium forming from the ekaosmium.

The filtrate from the separation of the bismuth was treated with hydrogen sulfide. The resulting sulfide precipitate was also very active, owing to the ekarhenium present. After about 3 to 4 hr. the amount of ekarhenium (No. 93) remaining was very low, and the decay curve (curve B) flattened rapidly, gradually approaching the value of 66 hr. for ekairidium. This curve likewise shows some evidence for the 5.7-hr. ekaosmium. This mixture contained about 2.7 times as much ekairidium as the bismuth precipitate.

The ekaosmium present at the time the metallic bismuth was reduced apparently was quantitatively precipitated, whereas only about one-third of the ekairidium precipitated.

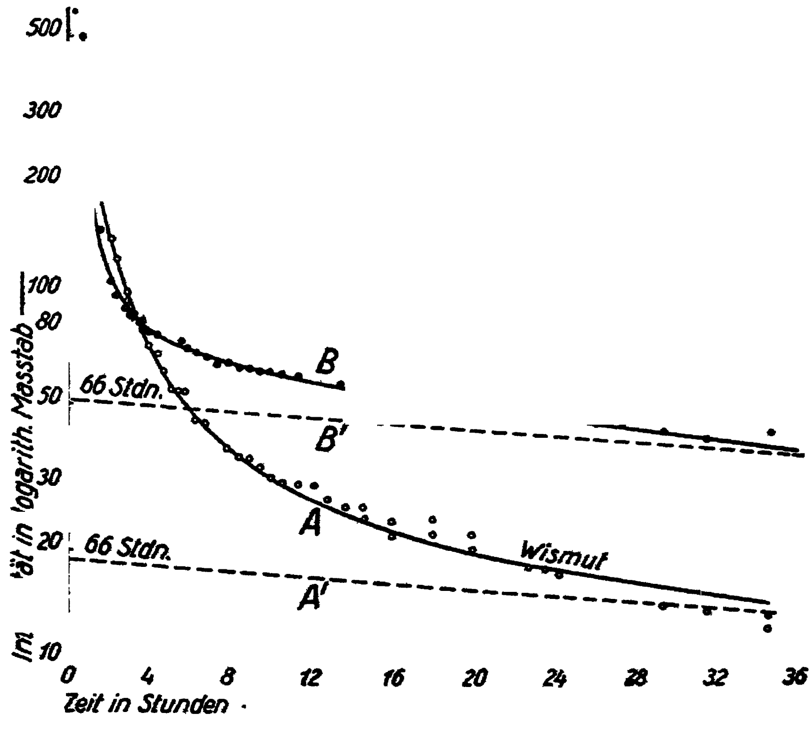


FIG. 3. The partial separation of ekairidium from ekaosmium, using the alkaline stannous chloride–bismuth salt reaction (according to Hahn, Meitner, and Strassmann (48)).

(*2*) *Partial separation of ekairidium and ekaosmium with sodium hydroxide.* Samples of uranium which had been bombarded for long periods of time in order to build up the concentration of ekairidium were treated with sodium hydroxide. It was observed that a considerable portion of the 66-hr. substance passed into the filtrate along with the ekarhenium, and that the precipitate contained an appreciable amount of the 59-min. ekaosmium. This compares well with the experiments on samples bombarded for short periods, which showed likewise that the ekaosmium precipitated. However, if large quantities of uranium were used in these experiments, the German investigators noted that the quantity of the eka-iridium adsorbed by the uranium precipitate increased. No quantitative results were obtained, the suggestion being that the presence of the eka-platinum of 2.5-hr. half-life interfered.

(3) The solubility of ekairidium sulfide in 10 N hydrochloric acid. Hahn, Meitner, and Strassmann (48) also studied the effect of hydrogen sulfide on ekairidium in solutions of varying hydrochloric acid concentration. A quantity (about 10 g.) of uranium was bombarded for 60 min. The usual sulfide precipitation from a 2 *N* hydrochloric acid solution, using platinum as a carrier, was made. The platinum sulfide was dissolved and allowed to stand for 2.5 hr. to permit the disintegration of the ekarhenium (16 min.). This solution, which was 10 *N* in hydrochloric acid and to which some perrhenate solution had been added, was again saturated with hydrogen sulfide in the cold. Part of the platinum and all of the rhenium precipitated. The filtrate, after dilution to 2 *N* concentration, was heated to boiling, and the remainder of the platinum precipitated as the sulfide. The decay curves showed that the ekaosmium (59 min.) which remained in the mixtures was almost quantitatively in the precipitated sulfide from the strongly acid solution, whereas none of the 59-min. material seemed to be in the precipitate obtained from the dilute acid solution. The activity curves were very complicated, since apparently four different kinds of atoms were present. The decay curves for each of the precipitates gradually changed over to the characteristic 66-hr. slope, indicating also about equal distribution of the ekairidium in each. The conclusion reached by the investigators was that ekaosmium can precipitate more readily in strongly acid solutions than can ekairidium.

(B). The separation of ekaplatinum (No. 96) from the other platinum group homologs

Hahn, Meitner, and Strassman conducted experiments to prove the existence of ekaplatinum. They bombarded uranium for days or weeks to permit a building-up of the elements of greatest atomic number. The transuranic elements were then separated by means of hydrogen sulfide, using platinum as a carrier. The precipitates were allowed to stand from 1 day to several days. The decay curves of these precipitates indicated that the ekarhenium (16 min.) and the ekaosmium (59 min.) had disintegrated, leaving only the 66-hr. element (No. 95) and its decomposition product, the 2.5-hr. ekaplatinum (No. 96). The 66-hr. substance seemed to be almost inactive. The formation of the ekaplatinum caused a very definite increase in the activity of the precipitate.

The German investigators suggested six different methods for separating ekaplatinum and ekairidium from mixtures which had been standing long enough to permit the complete disintegration of the ekarhenium and ekaosmium.

Method 1. Ekaplatinum was found to precipitate in very slight amount when a 10 N hydrochloric acid solution was saturated with hydrogen sulfide. In 2 N hydrochloric acid ekaplatinum was also not entirely precipitated. The increase in activity of a rhenium sulfide precipitate prepared from a 10 N hydrochloric acid solution suggested that about 75 per cent of the ekaplatinum (No. 96) remained unprecipitated.

The order of precipitation by hydrogen sulfide in a strongly acid solution is: eka-Os > eka-Re > eka-Ir > eka-Pt.

Method 2. Apparently only a small amount of ekaplatinum precipitated with bismuth when alkaline stannous chloride was used as the reducing agent. This separation of ekaplatinum from ekairidium seems to be more efficient than the precipitation with hydrogen sulfide.

At this point it should be mentioned that one would expect, from the periodic table relationships, that all of the platinum group homologs would be easily and completely precipitated along with bismuth using alkaline stannous chloride, even though the results of the German investigators seem to indicate the opposite. This again raises the question as to the exact structures and chemical properties of these elements of high atomic number. Are they members of a transition group or not? Could it also be that, in contrast to the structures proposed above, either ekaosmium or ekairidium is the first member of a new "inner transition" group and that ekaplatinum is exhibiting properties which might be expected of the second or third member of such a group?

Method 3. Ekaplatinum is apparently more volatile than ekairidium, according to Hahn, Meitner, and Strassmann. This information resulted from several different tests, as follows: (*a*) A precipitated mixture of platinum and rhenium sulfides containing an excess of ekairidium was carefully ignited in an open crucible. The activity of the residue in the crucible showed it to be almost pure ekairidium, the decay curve showing the eventual formation of ekaplatinum. (*b*) The transuranium elements were removed from uranium which had been subjected to a long period of bombardment by precipitation with hydrogen sulfide, with platinum as a carrier. The platinum sulfide was dissolved in aqua regia, and reprecipitated as the sulfide in order to eliminate traces of UX formed during the bombardment period. This preparation was then carefully ignited, the resulting mixture then being allowed to stand until the next day. The activity then showed an equilibrium between the 66-hr. ekairidium and the 2.5-hr. ekaplatinum.

A series of sublimations similar to those mentioned for the separation of ekaosmium and ekairidium was made on the above preparation. The first sublimate resulted from a 2.5-min. heating with a Bunsen flame. The second sublimate resulted from a 2.5-min. ignition with a blast lamp. The decay curve of the first sublimate showed a very definite excess of ekaplatinum (2.5 hr.). The activity curve gradually changed to show the formation of ekaplatinum from ekairidium.

A question which should be asked in connection with these fractional sublimation experiments is whether the elements themselves, or their oxides or sulfides, were volatilized? If it were the elements themselves, it indicates that these elements resemble metallic mercury in their tendency to volatilize somewhat readily. Such a tendency would also indicate that the physical properties of these elements are not the same as those predicted previously. Since the sublimations were made in air, it was probably the oxides that evaporated, especially for the low temperature ignitions. It could be possible to sublime these metals slowly in a blast lamp.

Method 4. The adsorption of ekaplatinum on precipitated ammonium pyrouranate. As mentioned previously (page 130), ekaosmium precipitates completely, whereas ekairidium (No. 95) is only partially precipitated upon treatment of the irradiated uranium solutions with sodium hydroxide. Experiments conducted on samples rich in the 66-hr. ekairidium and the 2.5-hr. ekaplatinum (No. 96) showed that the latter was even more soluble than ekairidium (66-hr.) in the basic solutions. The German investigators also noted that the tendency of the platinum homologs to coprecipitate or to be adsorbed with ammonium pyrouranate varied in the following order: eka-Os > eka-Ir > eka-Re > eka-Pt.

As in the precipitation of the sulfides from strong hydrochloric acid solutions, ekaosmium is the most easily separated or least soluble and ekaplatinum the least easily precipitated or adsorbed.

Method 5. The separation of ekaplatinum with platinum ammonium chloride. Seeking to learn if the platinum homologs formed were analogous to platinum ammonium chloride and iridium ammonium chlorides, Hahn *et al.* found that mixed crystals could be formed and that, in addition, a separation could be effected. A mixture of the 66-hr. ekairidium and the 2.5-hr. ekaplatinum was added to a dilute hydrochloric acid–platinum chloride solution, to which ammonium chloride was then added. Activity measurements showed that the 2.5-hr. material precipitated in the crystals formed, even though present in very slight amount. In another study ekairidium also crystallized, with ekaplatinum in definite excess. Thus it was shown that these elements are similar to the platinum group in forming the same typical salts, and that a separation of elements 95 and 96 could be made.

Method 6. The use of platinum foil for separating ekairidium. As mentioned earlier (page 127), ekarhenium could be separated from ekaosmium because the more noble character of the latter permitted its precipitation on a platinum foil. When a piece of platinum was placed in a solution containing a mixture of ekairidium and ekaplatinum, both metals were found in the plated deposit. Ekaplatinum was present in excess. Curve A in figure 4 indicates the activity of the materials plated on the platinum during a 10-min. immersion in a hot solution containing the transuranium elements (in this case, essentially only elements 95 and 96) in the presence of small amounts of lead, titanium, bismuth, and zirconium. Curve B records the activity of the sulfide precipitate obtained by treating the solution, remaining after the platinum foil was removed, with hydrogen sulfide. The trend of the curve shows the building-up of the 2.5-hr. ekaplatinum. (It must be remembered that, for equal numbers of atoms, the shorter lived ekaplatinum emits a greater number of particles per unit time than the more stable ekairidium.)

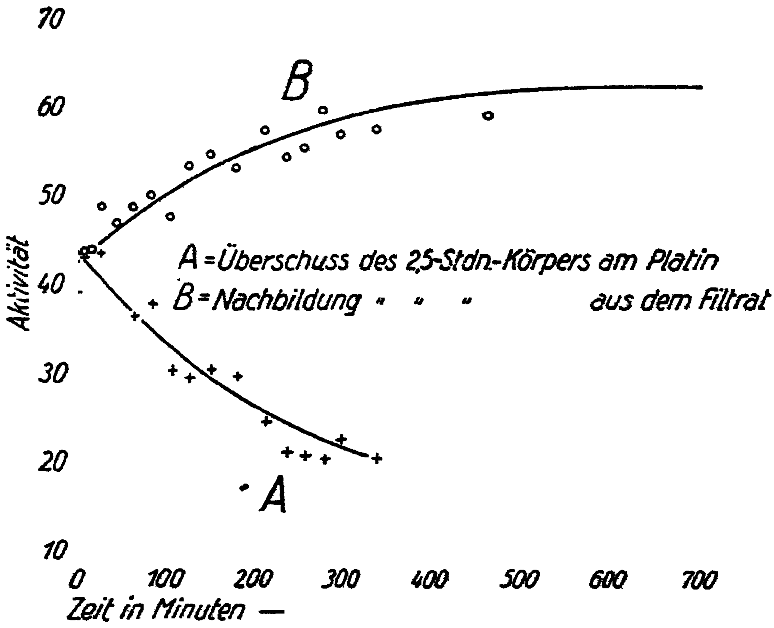


FIG. 4. The activity curves explaining the electrolytic separation of ekaplatinum from ekairidium (according to Hahn, Meitner, and Strassmann (48)).

Obviously these experiments of Hahn, Meitner, and Strassmann are not complete. Their excellent work, however, has paved the way for the establishment of the three different series formed and of the chemical nature of these various elements.

I. Curie and Savitch (18) have verified the greater portion of the results of the German group, although they stress that certain separations as outlined by Hahn *et al.* are difficult to carry out, that UX is very troublesome, and that all of the transuranium elements are produced under almost identical conditions. They observed and separated chemically the substances exhibiting half-lives of 16 min., 23 min., 59 min., and 2.7 days, their results being in accord with those of Hahn, Meitner, and Strassmann.

D. The existence of another transformation process

It will be recalled from the results of the German workers that difficulty was experienced, owing to an activity apparently associated with an element of atomic number less than 92. This behavior was finally explained as being due to a Szilard–Chalmers reaction.

The problem of counteracting the effect of UX was undertaken by I. Curie and Savitch (18), who used filters around their counter to absorb the β-rays of this element. A copper filter of 0.1 g. per cm.^{2} cross section was found to absorb one-half of the β-rays of UX, a 0.5 g. per cm.^{2} filter absorbed down to 5 per cent, and a 0.75 g. per cm.^{2} filter absorbed to about 2 per cent, this last residue being attributed to gamma rays. Accordingly they measured the radiations from bombarded uranium penetrating the copper filters of 0.5 g. per cm.^{2} The uranium preparations had been subjected to long periods of bombardment, the samples being in thick layers and large quantities (4 g. per 10 cm.^{2}).

For their activity measurements the French scientists used a compensating Hoffmann electrometer in measuring the ionization. Two thick uranium preparations, only one of which had been irradiated, were placed in two identical chambers connected with the electrometer. Hence the difference in the ionization currents produced was determined, the current due to the formation of UX being automatically compensated for during the experiment. For preparations bombarded over long periods of time, it was observed that the 3.5-hr. activity seemed to be dominant after the disappearance of the 16-min. activity. Their estimate of the number of β-particles emitted by the 3.5-hr. isotope, for thin preparations bombarded to saturation, was about one-fourth the initial number of β-rays from the 16-min. ekarhenium.

The periods observed were (*a*) two short periods (2 min. and probably the 40-sec. period); (*b*) the 16-min. period; and (*c*) a period of 3.5 hr. They have presented two explanations for this 3.5-hr. material, the earlier suggestion being that it was isotopic with thorium, and the more recent idea being that it is an actinium isotope.

Reviewing the first suggestion, the French investigators reported that the 3.5-hr. substance did not precipitate with hydrogen sulfide during the separation of uranium and the transuranium elements. The substance could be separated from uranium, however, apparently going with UX during the separation of this element from uranium. Since it seemed somewhat similar to UX in chemical behavior, and since UX presents difficulties in activity measurements, accurate determinations were extremely bothersome to make. The quantities of uranium used were large (15 to 20 g.); the presence of residual beta and gamma rays of UX affected the physical measurements.

I. Curie and Savitch (18) postulated, at first, that the 3.5-hr. substance was isotopic with thorium, and was formed by neutron bombardment with the emission of an alpha particle as follows:

$$^{238}_{92}\mathrm{U} + ^{1}_{0}n \rightarrow ^{235}_{90}\mathrm{R}_{3.5\,\mathrm{hr.}} + ^{4}_{2}\mathrm{He}$$

According to this scheme, the product of the disintegrating 3.5-hr. substance would be an isotope of protoactinium.

I. Curie and Savitch (18, 19) reported in both articles that this radioelement formed with both fast and slow neutron bombardment under almost the identical conditions for preparing the transuranium elements. Originally their thought was that the 3.5-hr. substance was a derivative of ekarhenium, because of the similarity in the conditions for producing these two active substances. The chemical separations indicated that they were not genetically related, and as a result the formation of the thorium isotope was suggested.

Since Hahn and Meitner could not find an isotope of thorium in the activated uranium, Curie and Savitch (19) investigated the 3.5-hr. material with still greater care. In this latter investigation they dissolved the irradiated uranium in hydrochloric acid, added some platinum and lanthanum, and finally ammonium carbonate. The lanthanum precipitate thus formed was redissolved in acid. A small amount of thorium (free from thorium X and the active deposit) was added to the solution, which was again treated with ammonium carbonate. This procedure was repeated twice. Uranium and those of the transuranium elements that are slightly soluble under these conditions were thus removed. Finally the precipitated lanthanum was redissolved in 2 *N* hydrochloric acid, some platinum added, and the remaining transuranic elements precipitated by hydrogen sulfide. The lanthanum fraction contained the 3.5-hr. substance and a trace of UX.

In their later report Curie and Savitch (19) stated that this active body (*a*) is not precipitated by hydrogen sulfide from 2 *N* hydrochloric acid, (*b*) is precipitated by ammonium carbonate, (*c*) is not precipitated by potassium iodate in concentrated nitric acid solution (difference between Th and UX), (*d*) is not precipitated by phosphoric acid from 2 *N* hydrochloric acid in the presence of zirconium (difference from protoactinium), and (*e*) is precipitated by oxalic acid from a weakly nitric acid solution in the presence of lanthanum (analogous to the rare earths and actinium).

These chemical properties caused the French workers to suggest that the material is either an actinium isotope or a new transuranium element possessing chemical properties entirely different from those of the higher homologs of rhenium and the platinum metals. Both hypotheses are difficult to visualize, and the investigators suggest that considerable more research will be necessary to clarify the problem.

Should the chemistry of this active substance as reported by I. Curie and Savitch prove to be correct, one might conjecture as to the possibility of *K*-electron capture in addition to the emission of an alpha particle to explain the transition from uranium to actinium as a result of neutron bombardment. To change from uranium to actinium, the atomic number must be decreased by three units. This may be effected by having either a proton or a positron and an alpha particle emitted; or a *K*-electron capture in conjunction with alpha emission must occur. A possible reaction might be

$${}_{92}\mathrm{U} + {}^{1}_{0}\mathrm{N} + (K\text{-electron}) \rightarrow {}_{89}\mathrm{Ac} + {}^{4}_{2}\mathrm{He}$$

Naturally it is impossible to consider the masses involved.

The evidence favoring *K*-electron capture is very meager. To begin with, no elements beyond erbium (No. 65) have been found to exhibit positron emission, this latter effect often being associated with the electron capture. Furthermore, the fairly conclusive evidence for the 10 sec.-, 40 sec.-, and 23 min.-isotopes of uranium is indicative that the *K*-electron capture probably would be very difficult to bring about. These short periods indicate that it is relatively easy to activate the uranium for the formation of the three transformation series suggested by Hahn. Also, there is no evidence of *K*-electron capture in the natural radioactive series, which includes these same elements. This conjecture is worthy of consideration only if no definite evidence of a simpler type of change is observed.

Hahn and his coworkers have not reported any evidence of the 3.5-hr. material. It is entirely possible that these investigators might have had the correct mixture of the 3.5-hr. substance along with certain of the naturally occurring isotopes (including the 6.7-hr. UX) to give decay curves which might not, on first analysis, have given any indication of the 3.5-hr. element. The question is still open.

A meager amount of additional evidence for the existence of the 3.5-hr.

substance is indicated in some unpublished work of Pool (68). Metallic uranium was bombarded for 6.5 hr. with fast neutrons produced by the lithium–deuteron reaction. The deuteron source was the Michigan cyclotron. Both the beta and the gamma activities of the uranium were determined. The beta decay curves showed an intense 3.7-hr. activity. The gamma decay curves showed a 3.3-hr. activity for the same sample. The changing slope of the curves would easily lead one to believe that the period could be 3.5 hr., which would agree with the results of Curie and Savitch. No chemical separations were made, all results being strictly dependent on the activity measurements. The intensity of the neutrons developed with the cyclotron is tremendously greater than that of the radon–beryllium sources, hence it is conceivable that this method might intensify processes difficult to bring out by the lower energy sources. I. Curie and Savitch report that their sources gave about 300 to 1000 millicuries with 13 M.e.v. as the upper limit for neutrons. The intensity of neutrons from the lithium–deuteron reaction (with the cyclotron) is several Curies with about 20 M.e.v. as the upper limit for neutrons.

The 3.5- and 3.7-hr. periods found by Pool are dominant over the extremely short-lived periods. For the strongly activated uranium (bombardment for 6.5 hr. with fast neutrons) the intensity of the beta emission was approximately 23 μc, with a saturation value of 33 μc. This intensity was recorded after the short-lived substances had completely disappeared. This observation of the dominant nature of the 3.3- to 3.7-hr. periods by Pool corresponds to the observations of the French investigators.

Abelson (1), using the Berkeley cyclotron, activated uranium with neutrons, and reported that the extensive work of Hahn was verified, for the most part, by his results. The emitted particles were found to be negative in all cases. He verified the contention that at least two separate chains of β-emitting substances result from the activation of uranium by thermal neutrons. In addition to the periods reported by the French, Italian, and German groups, Abelson reported the detection of a 17-hr. period. Activated material was examined for α-particles within 5 min. after cessation of bombardment, using a linear amplifier. It was concluded that α-active isotopes of half-life periods less than 1000 yr. were not present in amounts comparable to the β-active isotopes.

A 16.3-hr. period was noted by Pool (68), which might correspond to the above 17-hr. period. Abelson did not report a 3.5-hr. activity.

E. The energy relationships involved

The German group has made an exhaustive survey of the energy relationships necessary to activate uranium and bring about the different transformation series. In contrast to the suggestion of Curie and Savitch, they have no definite evidence of alpha emission. They report only the chains of β-particles, which is an effect not observed in the natural disintegration series.

Meitner *et al.* (63) used a Geiger-Müller counting tube of aluminum of 0.1 mm. wall thickness and an amplifying system when determining the genetic relationships. Their counters were built into thick lead chambers into which the preparations were placed in small lead boats.

To observe the very short-lived uranium isotopes, UX-free uranium preparations were bombarded for very short periods (15 to 60 sec.) with fast neutrons to avoid formation of the 23-min. isotope. In figure 5 curve A is the activity for a 13-sec. bombardment; curve B for 30 sec.

The existence of several substances of very short periods is suggested. In curve B the slope indicates the presence of a 2.2-min. material, shown to be ekarhenium chemically. Subtracting this value, the resultant is curve B, which likewise is not straight. It indicates that a 40-sec. period is present. Making another subtraction curve B results, which is a straight-line exponential of 10-sec. half-life. This and the 40-sec. value are characteristic of two different isotopes of uranium, as proven chemically. These being the shortest periods and not chemically separable from uranium, they must head the families. The quantity of the 2.2-min. substance is affected by the period of irradiation, hence it must be a disintegration product of the 10-sec. uranium.

By varying the time of bombardment the Germans showed that the 16-min. substance was a disintegration product of the 40-sec. uranium. Since beta emission occurs, according to the radioactive displacement laws, the only possibility for the new element formed would be an element 93, ekarhenium. This verifies the original declaration by Fermi that transuranium elements are formed. The chemical separations made by both the Italian and German groups substantiate the contention.

Using longer irradiation periods, Meitner *et al.* proved that the 59-min. activity was due to an ekaosmium isotope formed from the 2.2-min. ekarhenium, and that the 66-hr. active principle (ekairidium) changed into ekaplatinum of 2.5-hr. half-life. Ekaplatinum was essentially inactive.

The German group reported that materials subjected to extremely long periods of bombardment exhibited a very weak but detectable alpha emission in a Wynn-Williams proportional amplifier. No evidence of α-activity was noted for any material subjected to short periods of bombardment. The suggestion made was that a long-living alpha-emitter, whose genetic relationship has not been determined, results from long bombardment.

Likewise the evidence showed that the 16-min. ekarhenium changed to the 6-hr. ekaosmium. Earlier the value was given as 10 to 12 hr., then as 6, and the newer value as 5.7 hr.

Whether ekairidium is formed from this ekaosmium isotope is still a question. If active, the ekairidium is probably very long-lived. Meitner, Hahn, and Strassmann suggest that some of their residues have exhibited a very long period.

For the third process (see page 126), evidence has been secured for only one transformation product, a beta-emitting uranium isotope of 23-min.

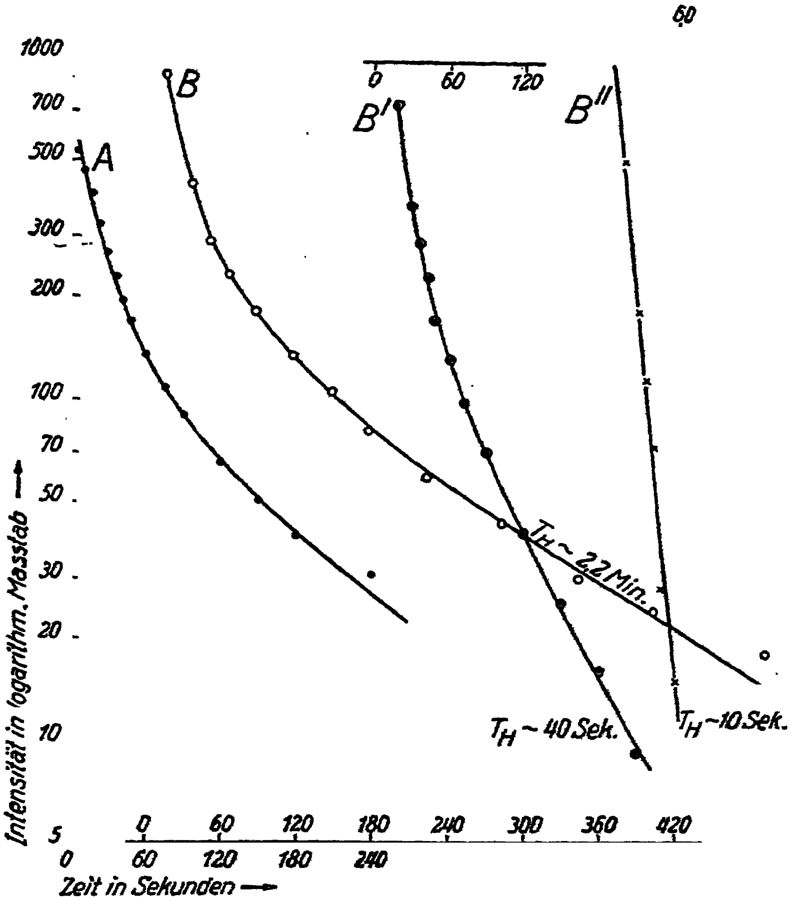


FIG. 5. The activity curves showing the existence of the 10-sec., the 40-sec., and the 2.2-min. active substances (according to Meitner, Hahn, and Strassmann (63)).

period, which goes into ekarhenium. The latter may be long-lived. The 66-hr. substance mentioned above is definitely not related to this ekarhenium because the former substance results from fast neutron bombardment, whereas the 23-min. uranium isotope results only from slow neutron irradiation.

1. The effect of fast and slow neutrons

After Fermi and Amaldi (35, 7) reported that different effects were obtained with fast and slow neutrons, Meitner, Hahn, and Strassmann (63) began a systematic study of the effect of slow and fast neutrons on uranium. They wished to observe the energies of the neutrons effecting the three transformation processes, and to determine the effect of filters on processes I and II.

Both processes I and II resulted from irradiation with fast as well as with thermal neutrons. When a cadmium filter was used during activation by fast neutrons the same relative intensities were always obtained. With slow neutrons the yield of active materials was made as follows: A paraffin cylinder of about 20 cm. cross section and 20 cm. length, with the neutron source (several radon–beryllium tubes) placed in the middle, was utilized. The preparations being studied were bombarded through different thicknesses of paraffin. Also, bombardments were made with and without a cadmium filter under 4 cm. of paraffin. The intensity of the activity was found to be reduced to about 87 per cent when a 0.42-cm. thick cadmium filter was placed on both sides of the uranium. Therefore, about 90 per cent of the activation was produced by thermal neutrons. This indicates also that the 66-hr. ekairidium (No. 95) and the 2.5-hr. ekaplatinum (No. 96) belong to process I or II and not to process III. The same result was noted after long bombardment (21 hr.) with and without the use of the cadmium filter. The concentration of the same two substances was decreased, in both cases, in the same proportion as the shorter-living uranium isotopes.

The German investigators reported that they were unable, within the limits of error, to detect any difference in the intensity for processes I and II using either thermal or rapid neutrons.

A series of experiments was performed in which (*a*) the uranium preparation was surrounded by paraffin, (*b*) a layer of paraffin was placed only between the sample and the neutron source, and (*c*) a cadmium filter was used for comparison experiments in studies *a* and *b*. With the uranium imbedded in paraffin, and using a cadmium filter, the activation was decreased to 21 per cent. That is, 80 per cent of the activation resulted from thermal neutrons and 20 per cent from fast neutrons. With paraffin only between the sample and the neutron source, bombardments, with and without the cadmium filter, showed that the induction was only 25 per cent, since thermal neutrons were eliminated by this treatment.

That the intensity of both processes I and II was the same even when the thermal neutrons were filtered makes it very probable that no resonance absorption exists in the energy ranges intermediate between fast and thermal neutrons. Beryllium neutrons possess definite energies between

10^5 to about 14×10^6 volts. Hence a definite statement of the effective energies of the fast neutrons is difficult to make. The measurements with fast neutrons *with* and *without* the cadmium filter always gave similar results. Thus the neutron sources did not give off primarily thermal neutrons.

Comparison experiments were also made by the German investigators, using thicknesses of uranium preparations ranging from 61 mg. of uranium per cm.^{2} to 1.27 g. of uranium per cm.^{2}, and with a cadmium filter 0.46 mm. thick. The intensities with and without the filter were again the same within the limits of experimental error.

The practical significance of these determinations is that one can bombard very thick layers of uranium with rapid neutrons to obtain an evenly activated product.

Filters possessing very definite resonance absorption regions in the range from 1 to several volts and which absorb thermal neutrons to only a slight degree did not cause any decrease in the intensities of the two processes.

2. The effective neutron energy for process III

Relatively large amounts of uranium were used for this determination, since only one uranium isotope is detected in the activated material. Using identical conditions for all of their experiments, as far as the amounts of uranium, etc., were concerned, it was shown that about 65 per cent of the activation was due to other than thermal neutrons when the uranium was imbedded in paraffin with a 4-cm. thickness of paraffin between the neutron source. Process III is therefore caused by slow neutrons.

To ascertain whether the activation by slow neutrons was due to resonance, the German group measured the auto-absorption in uranium. A thin layer of the uranium preparation containing 43 mg. of uranium per cm.^{2} was bombarded with neutrons, the source of which was but a short distance from the sample. The use of a cadmium filter decreased the intensity of activation about 5 per cent, indicating that 95 per cent of the intensity was certainly not due to thermal neutrons. A uranium filter of 61 mg. of uranium per cm.^{2}, used with and without the cadmium, diminished the intensity by neutrons other than thermal neutrons by about 31 to 34 per cent. This gave a mean mass absorption coefficient of $\mu/\rho = 7$ cm.^{2} per gram, due to strong absorption in the uranium. Allowing for the angle at which the neutrons travelled, the actual mass coefficient was calculated as $\mu/\rho = 3$ cm.^{2} per gram. The coefficient for thermal neutrons, as determined by Dunning (26) and his coworkers, was found to be 0.1 cm.^{2} per gram. Thus the slow neutrons causing activation of the uranium show a mass coefficient of absorption at least thirty times greater.

Meitner *et al.* (63) also determined the energy of the resonance neutrons by comparing the absorption of these neutrons in boron with the value for thermal neutrons in boron using the same experimental conditions. For this calculation the relationship

$$E_I = E_{\text{th}} \left(\frac{\mu_{\text{th}}}{\mu_R}\right)^2$$

may be used. μ_{th} is the absorption coefficient of the thermal neutrons in boron, the value of which was determined by Rasetti and Goldsmith (69). μ_R is the resonance absorption coefficient and was determined by Meitner. The resonance energy was found to be 25 ± 10 e.v., which is the resonance level of the slow neutrons activating process III.

$$_{92}\text{U} + n \rightarrow {}_{92}\text{U}; \qquad {}_{92}\text{U} \xrightarrow[\text{23 min.}]{\beta} {}_{93}\text{Eka-Re}$$

3. The energy of the emitted beta rays

Meitner (61) made a careful study of Wilson photographs of the sulfide precipitates obtained from preparations bombarded for different periods in order to determine the β-particle energies. The analysis of over 400 β-emissions showed a range from about 3200 kv. to 600 kv. In noting which products were present at any instant with the corresponding time of β-emissions, it was concluded that those emissions ranging from 1000 kv. upward, with the maximum of the beta-ray spectrum in the neighborhood of 3200 kv., were due to eka-$\text{Re}_{93}^{16\text{ min.}}$. The eka-$\text{Os}_{94}^{59\text{ min.}}$ has fewer penetrating primary β-emissions, the limit for the more rapid betas being about 600 kv. For samples bombarded for several months, it was decided that the maximum of 700 kv. observed was due to the β-particles from eka-$\text{Pt}_{96}^{2.5\text{ hr.}}$, since eka-$\text{Ir}_{95}^{66\text{ hr.}}$ is very feebly β-active.

Curie and Savitch (18) found slightly different results in their β-ray study. For eka-$\text{Re}_{93}^{16\text{ min.}}$ they report two groups of beta particles, one resembling those of UX, and in the range of 2×10^6 e.v., representing 90 per cent of the intensity; the other is very penetrating and mixed with gamma radiation. They suggest that Meitner's value of 3×10^6 e.v. may probably correspond, not to the upper limit of the spectrum, but to the lower region of the penetration group. They also comment that the energies of the β-rays of the 2-min. and the 3.5-hr. substances should be at least of the order of 6×10^6 e.v.

F. The processes of formation of the artificial radioelements

Since the experimental evidence indicates three and perhaps four separate disintegration series resulting from irradiated uranium, it does not seem possible to interpret the numerous radioelements without calling upon the hypothesis of isomerism. Accordingly, for the moment, three processes will be postulated as follows:

$$ {}^{238}_{92}\mathrm{U} + n\begin{Bmatrix}\text{fast}\\ \text{slow}\end{Bmatrix} \rightarrow {}^{239}_{92}\mathrm{U} \xrightarrow[10\text{ sec.}]{\beta} {}^{239}93 \xrightarrow[2.2\text{ min.}]{\beta} {}^{239}94 \xrightarrow[59\text{ min.}]{\beta} $$

$$ {}^{39}95 \xrightarrow[66\text{ hr.}]{\beta} {}^{239}96 \xrightarrow[2.5\text{ hr.}]{\beta} {}^{239}97 \qquad \text{(I)} $$

$$ {}^{8}_{2}\mathrm{U} + n\begin{Bmatrix}\text{fast}\\ \text{slow}\end{Bmatrix} \rightarrow {}^{239}_{92}\mathrm{U} \xrightarrow[40\text{ sec.}]{\beta} {}^{239}93 \xrightarrow[16\text{ min.}]{\beta} {}^{239}94 \xrightarrow[5.7\text{ hr.}]{\beta} {}^{239}95 \rightarrow ? \qquad \text{(II)} $$

$$ {}^{238}_{92}\mathrm{U} + n\,(\text{slow}) \rightarrow {}^{239}_{92}\mathrm{U} \xrightarrow[23\text{ min.}]{\beta} {}^{239}93 \qquad \text{(III)} $$

It is noted that the mass number assigned to the radioelements is 239 in each case. One might ask why an atom of mass 237 is not suggested. This would be in accordance with observed experimental facts that under fast neutron bombardment two neutrons are ejected and the resulting element has a mass one less than the original, represented as follows:

$$ {}^{M}_{Z}\mathrm{R} + {}^{1}_{0}n\,(\text{fast}) \rightarrow {}^{M-1}_{Z}\mathrm{R} + 2\,{}^{1}_{0}n $$

No experimental evidence thus far indicates such a possibility. In most cases bombardment of a given element with fast neutrons and then with slow neutrons will give two different periods, thus enabling the investigator to say with certainty which change is occurring, an increase or a decrease of one unit in atomic weight. Such a procedure is a standard method for identifying those isotopes giving rise to the various observed periods. However, as already mentioned, the intensities of the activities noted for both fast and slow neutron irradiation of uranium are essentially the same. This means, therefore, that processes I and II are very probably isomeric. Thus if the atomic mass is 239 for process I it must be the same for process II.

There can be no doubt about process III, since it is a simple neutron capture of the type

$$ {}^{M}_{Z}\mathrm{R} + {}^{1}_{0}n \rightarrow {}^{M+1}_{Z}\mathrm{R} $$

Thus the first members of these series are isomers (isobaric isotopes).

Since processes I and II represent long isomeric series it is logical to inquire if it is possible for one isomeric nucleus to change to a second isomeric nucleus by liberation of energy. Such a transformation is not at all improbable, since either gamma emission or prohibited beta-particle transition is possible. Gamma rays have been recorded by Meitner, Pool, and others in their studies. It is also very probable that the β-ray transition of ekaplatinum to ekagold is a prohibited transition (due to a change of impulse momentum). The studies by Meitner on the γ-emission showed that the ekaosmium (59 min.) exhibited a much more intense γ-radiation than did ekarhenium (16 min.), these elements being in the different isomeric series. This indicates, if the Weiszacker representation is correct, that process I starts from a metastable state of U^{239}, whose impulse momentum must be considerably greater than that of the U^{239} which heads process II.

Another manner of looking at this concept is to assume that X, Y, and Z are three members of a disintegration series, and that X^1, Y^1, and Z^1 are the corresponding nuclear isomers of lower energies. Transformations such as $X \xrightarrow{\beta} Y$; $X^1 \xrightarrow{\beta} Y^1$, etc., are normal radioactive changes. There is also the possibility of changes such as $X \xrightarrow{\beta} Y^1$ and $Y \xrightarrow{\beta} Z^1$, probably associated with γ-emissions.

Other probable changes are transitions such as $X \xrightarrow{\gamma} X^1$, $Y \xrightarrow{\gamma} Y^1$, $Z \xrightarrow{\gamma} Z^1$ which might occur, especially if the energy differences between the metastable and the stable isomeric nuclei are small in comparison with the energies of emission of beta rays. With respect to processes I and II, it could be conjectured that one of these families is more metastable than the other, thus leading to transitions between the two. As Curie and Savitch point out, one might assume that the 66-hr. substance of process I might be formed in part from the 5.7-hr. element 94 of process II, since there is no definite evidence permitting complete verification of the change that Hahn *et al.* have postulated, namely, that the 66-hr. material is a product of the 59-min. ekaosmium.

Naturally active uranium is a mixture of three isotopes, 234 (UII), 235, and 238 (their relative abundance is 0.007:0.00006:1), any of which might be activated. Processes I and II result from fast neutron (also slow) bombardment. Meitner *et al.* have shown the effective cross section (for U^{238}) to be 1.6×10^{-25} cm.^{2} Isotopes 234 and 235 are probably not the parent substances of processes I and II, because the magnitude of the effective cross section would need to be so great that fast neutrons would be entirely ineffective. Both processes must start from U^{238}.

Process III probably can not originate from U^{235}, since from the measured absorption coefficients in uranium the resonance absorption cross section should be about $3{,}000{,}000 \times 10^{-24}$ cm.^{2}, which is considerably greater than $\lambda^2/4\pi$, where λ is the proper de Broglie wave length. It is probably a simple capturing process originating also with U^{238}, thus giving a third isomeric nucleus U^{239}.

That one of these processes may result in a series of mass number 238 can not be disregarded. Such a family could be headed by U^{238}, which is changed to a metastable state from the stable U^{238} merely as a result of absorbing some energy from the neutrons without capturing one of the particles or losing one from its own nucleus. Such a possibility could be proven by subjecting uranium to gamma radiation of high energy.

There is no doubt whatsoever that considerable more thought and research must be done before one can state definitely which isotopes are involved in these transformations, how the series are related, and what the energies involved are.

VI. SUGGESTED FUTURE STUDIES ON THE TRANSURANIUM ELEMENTS

The interesting puzzle of the transuranium elements is only partially solved. The excellent work of the scientists who have been investigating this field has contributed to the solution, but at the same time has brought forth new questions to be answered. A few suggested factors which should be investigated are the following:

1. Now that some of the chemical properties of ekarhenium are known, minerals should be investigated for the presence of this element. The probability of discovery is very slight, but the possible existence of an isotope of 93 of exceptionally long half-life should not be overlooked.

2. An exhaustive study of these elements should be made, using intense sources of neutrons (available at those places having cyclotrons, such as the Universities of California, Michigan, Rochester, etc.) Long and short bombardments should be made so that a very complete range in the activating periods may be utilized.

3. A study using monokinetic sources of neutrons (such as those produced with the deuteron–deuteron reaction) may produce valuable information about certain of the energy changes involved.

4. The investigations on the emission of α-particles, which have been started, should be extended, using the more energetic neutron sources.

5. Careful observations should be made to ascertain whether alpha particles, positrons, etc., are being emitted only during the bombardment period. The evidence on this point up to the present is negative.

6. Special precautions should be taken to observe whether any exceptionally long-lived substances which are very feebly active are formed.

7. The possible formation of isotopes of thorium, protoactinium and other elements of lower atomic number demands further study.

8. The bombardment of uranium with intense gamma radiation should permit, if activation resulted, a definite statement as to whether one of the disintegration series mentioned earlier has a U^{238} isotope as the head of the family. Perhaps gamma activation might give rise to still other series.

9. Deuteron bombardment is known to activate uranium. Owing to

TABLE 13

A summary of the properties of the transuranium elements

(Based essentially on the work of Hahn, Meitner, and Strassmann)

	SIMILARITIES	DIFFERENCES
Rhenium and ekarhenium.	Neither is precipitated from acid solution on the noble metals (Pt) Neither is precipitated by metallic bismuth in alkaline solution Both are quantitatively precipitated by hydrogen sulfide from hydrochloric acid solutions of moderate concentration, and are not so easily precipitated from highly acid solutions Both are precipitated by nitron Both are volatile as the oxide or the chloride at high temperatures	Ekarhenium is not volatile from a sulfuric acid solution even in the presence of a stream of hydrogen chloride
Osmium and ekaosmium...	Both are precipitated by metallic bismuth in alkaline solution Both are quantitatively precipitated by hydrogen sulfide even from strongly acid solutions Both are quantitatively precipitated by sodium hydroxide Both are volatile as oxides at higher temperatures	Ekaosmium does not distill from a nitric acid solution Ekaosmium is precipitated from acid solutions by platinum
Iridium and ekairidium..	Both separate with metallic bismuth in alkaline solution Both are almost completely precipitated by hydrogen sulfide from weak hydrochloric acid solutions	Ekairidium is appreciably volatile when heated strongly Ekairidium precipitates on platinum from acid solutions Ekairidium does not tend to form mixed crystals with platinum ammonium chloride to any extent Ekairidium is only partially precipitated by sodium hydroxide

TABLE 13—*Concluded*

	SIMILARITIES	DIFFERENCES
Platinum and eka-platinum............	Both precipitate well from hydrochloric acid solutions of not too high a concentration Mixed crystals of ammonium platinum chloride and ammonium eka-platinum chloride may be formed Both are incompletely precipitated by sodium hydroxide	Ekaplatinum as the oxide is appreciably volatile when ignited gently Ekaplatinum is precipitated from acid solution by platinum

TABLE 14

Observed beta-emitting transformation products

ISOTOPE	HALF-LIFE PERIOD	INVESTIGATORS
92 Uranium	10 sec., 40 sec., 23 min.	Hahn *et al.*
	10 sec., 40 sec., 23 min.	Fermi *et al.*
	40 sec., 23 min.	Curie and Savitch
93 Ekarhenium (Ao)	2.2 min., 16 min.	Hahn *et al.*
	2.2 min., 13 min.	Fermi *et al.*
	2 min., 16 min.	Curie and Savitch
94 Ekaosmium (Hs)	59 min., 5.7 hr.	Hahn *et al.*
	59 min., 10 hr.	Fermi *et al.*
95 Ekairidium	66 hr.	Hahn *et al.*
	3 days	Fermi *et al.*
	2.7 days	Curie and Savitch
96 Ekaplatinum	2.5 hr.	Hahn *et al.*
	2.5 hr.	Fermi *et al.*
Actinium, thorium, or protoactinium or ?	3.5 hr.	Curie and Savitch
	3.3–3.7 hr.	Pool
?	17 hr.	Abelson
	16.3 hr.	Pool

the fact that elements of low atomic weight are very easily activated by deuterons, traces of these elements in uranium could cause extreme difficulty. Deuteron bombardment might be of value in helping to establish the various transformation series.

10. Although not highly probable, the capture of *K*-electrons by the nucleus should be studied. The suggestion given in certain theoretical considerations that there must be a point at which the volume of the nucleus and that of the *K*-electronic orbit approach the same value lends strength to this idea. On the other hand, the fact that no *K*-electron capture has been observed in connection with the naturally radioactive series and that there is no definite evidence of positron emission beyond erbium ($Z = 68$) tends to indicate that *K*-electron capture in uranium is not very probable.

11. The chemical and physical properties of these elements require further study so as to effect a better correlation of their properties with those of the known elements, as well as to enable scientists to perfect the methods of separation and identification necessary in these studies of the artificially produced radioelements.

12. The entire field of energy relationships involved requires further study. The results thus far obtained are not as indicative as they might be of the various relationships existing between energies of activation, of disintegration, etc.

VII. A SUMMATION OF THE PROPERTIES OF THE TRANSURANIUM ELEMENTS

The properties of the transuranium elements are summarized in table 13. In table 14 are given the observed beta-emitting transformation products.

VIII. SUMMARY

1. No evidence of the existence in minerals of elements beyond uranium has been established.

2. A number of conjectures as to the total number of possible elements have been published.

3. Predictions of the properties of elements beyond uranium have been postulated.

4. Uranium may be readily activated by neutrons. The contention of Fermi that transuranic elements resulted from the disintegration of the activated uranium has been substantiated by workers in his own laboratory, by Hahn, Meitner, and Strassmann, by Curie *et al.*, by Abelson, and others.

5. Three isomeric nuclear series have been postulated to explain the observed transformations. A fourth process involving alpha radiation

and the formation of isotopes having atomic numbers less than 92 can not be overlooked.

6. Energy studies of the transformation processes have been made, but the results as yet are not sufficiently adequate and conclusive to explain all effects involved.

7. The chemical properties of these radioelements have been established sufficiently accurately and carefully to permit of separation and identifications. The chemistry of these elements is complex and not yet perfected.

8. The study of these elements is complicated by the chemical and the radioactive character of the other elements in this region of the periodic classification.

9. The continuous liberation of beta particles in processes I and II is a very interesting phenomenon. It has no counterpart in the natural radioactive series.

10. The names "ausonium" (Ao) and "hesperium" (Hs) have been mentioned by the Italian investigators for elements 93 and 94, respectively.

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THE ALKALI METAL CESIUM AND SOME OF ITS SALTS[1]

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The alkali group of metals in the order of increasing atomic weight comprises lithium, sodium, potassium, rubidium, and cesium. The metal cesium is the rarest one of the group and is also the most electropositive. It was discovered by Bunsen and Kirchhoff in 1860, by means of the spectroscope. Cesium was named by them after the Latin word "caesius," meaning "sky-blue," since the two prominent blue lines of its spectrum were most characteristic.

Cesium is found in very small amounts in a number of minerals: for example, in lepidolite, a lithia mica; in carnallite, a hydrous chloride of potassium and magnesium; and sometimes in beryl, a beryllium aluminum silicate. However, the most important source is the mineral pollucite, a silicate of aluminum and cesium which can contain as high as 42.5 per cent of cesium oxide on the basis of the formula $2Cs_2O \cdot 2Al_2O_3 \cdot 9SiO_2 \cdot H_2O$.

Breithaupt had found in 1846 two minerals constantly associated in small cavities in the Isle of Elba granite. He applied to them the names of Pollux and Castor, famous in mythology for their inseparable companionship. The cesium ore he called pollucite and its companion he called castorite. The latter is now known as petalite. It is a lithium aluminum silicate and is the same material in which lithium was discovered in 1817 by Arfvedson.

Pollucite in appearance is often clear and colorless, somewhat resembling quartz. Sometimes it is translucent to opaque with a fine-grained structure resembling massive beryl; occasionally it appears dull and almost gumlike externally. It is not easily recognized by casual inspection and probably many small deposits of it are passed unnoticed in the working of some granite pegmatite dykes for their various values. Pollucite has a hardness of 6.5 and a specific gravity of 2.88–2.90 when the material is high grade in quality.

In 1891 a single cavity of pollucite was found at Hebron, Maine, the dimensions of which were 3 ft. x 6 ft. x 1½ ft. It yielded about a pound of pollucite, which was described and analyzed by H. L. Wells (6). The ore occurred in fragments mixed with clay and associated with quartz and a cesium-bearing beryl. In appearance it was similar to the Elba mineral. The unusually large amount of it obtained from this source in Maine enabled Wells and Penfield to make some important researches upon the cesium trihalides.

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Prior to the recent development during the past ten years (*1*) of the low voltage light of the Claude Neon type, (*2*) of the vacuum tube for radio work, and (*3*) of the photoelectric cell, cesium and its salts were regarded as laboratory curiosities. During 1926 and 1927 a demand for cesium developed from the manufacturers of radio tubes, and prices ranging up to $15.00 per pound were reported for average-grade pollucite ore. This greatly stimulated prospecting activities and the demand was partially met by the small deposits uncovered in Maine. With the introduction on the market of the electric radio set and the consequent change in types of tubes, the demand soon fell off and the prices declined accordingly. Without doubt, the greatest strike of pollucite ore that has, to date, been removed from the earth's crust was found at the Tin Mt. Mine near Custer in the Black Hills of South Dakota. During the fall of 1927 this mine, owned and operated by the Maywood Chemical Works of Maywood, New Jersey, was opened for the primary purpose of developing lithium ore reserves for that Company. In the course of development work, consisting principally in the drilling of underground prospecting tunnels, at least four separate and distinct "pocket" formations of pollucite ore were discovered within a radius of 75 ft. Mining operations at Tin Mt. were discontinued in 1930 and to date have not been resumed. In all, over 100,000 lb. of cesium ore have thus far been obtained from this source. It has varied considerably in quality and some lots, being so altered in ages past by the geologic leaching of their alkali value, have run as low as 1 per cent cesium oxide. However, considerable ore with a cesium oxide content as high as 32 per cent was found. This Tin Mt. mine, a granite pegmatite deposit, has been described in the literature by G. M. Schwartz (5), Joseph P. Connolly (1), and others.

Pollucite, being a type of silicate mineral that is decomposable by mineral acids, is best processed for its cesium value by the direct treatment of the finely powdered ore with either hydrochloric or sulfuric acid, the choice depending somewhat upon the ultimate salt desired as finished product. The original methods for the extraction and purification of cesium from pollucite are largely the work of H. L. Wells. The essentials of his procedure consist in extracting the mineral with concentrated hydrochloric acid, dehydrating the silica in the extract, and precipitating the cesium values either as cesium lead chloride ($2CsCl \cdot PbCl_4$) by the addition of lead nitrate (7), or as cesium antimony chloride ($3CsCl \cdot 2SbCl_3$) using antimony chloride (9). The use of the latter as a specific reagent for the precipitation of cesium salts had first been applied by Godeffroy (2). The lead chloride method had been devised by Wells, but in dealing with the crude extracts from pollucite ore it was later discarded because he found that while it was very convenient and efficient for removing small quantities of cesium from all sorts of solutions, it was inconvenient in cases where large amounts of cesium were concerned. Having obtained the double salt of cesium antimony chloride, Wells decomposed it either by suspending it in water and passing in hydrogen sulfide, which procedure he admitted was a slow and laborious operation, or he precipitated the antimony from the double salt by the addition of ammonium hydroxide. This produced large quantities of ammonium chloride, the removal of which was a serious drawback, not only because it was a very slow operation but because it introduced the danger of losing appreciable quantities of cesium chloride in the subsequent removal of the ammonium chloride by volatilization. Wells eliminated this shortcoming by converting the chlorides to nitrates by the addition of nitric acid and then entirely destroying the ammonium salts present by heating the solution until there was no further evolution of gas. The nitrates were then converted to the carbonates by adding two parts of oxalic acid and evaporating to dryness. On subsequent ignition the cesium oxalate was broken down completely at red heat into cesium carbonate, which was then dissolved in water, and separated by filtration from the insoluble traces of iron, aluminum, and antimony together with the carbon formed in the ignition. In this manner he finally obtained the cesium carbonate in pure form.

In 1924 Lenher, Kemmerer, and Witford (4) made some modifications in the Wells procedure of extracting the cesium values from pollucite. One change consisted in extracting the dry residue, obtained in the silica dehydrating operation, with hydrochloric acid of a concentration that would render least soluble the cesium antimony chloride subsequently formed. This concentration in their experience was 3 normal acid. They also hydrolyzed the cesium antimony salt by boiling with water, thereby directly obtaining a product which contained only small quantities of antimony along with traces of iron and aluminum, once the bulk of the precipitated antimony salts had been removed by filtration. They finally obtained the cesium in the form of pure cesium carbonate, after converting the chloride to the nitrate and then to the oxalate according to the procedure of Wells, the yield of carbonate from the pollucite ore used by them amounting to 37 per cent.

In the problem of the large scale extraction of cesium values from many tons of the pollucite ore found at Tin Mt., the finely divided ore was treated with hydrochloric acid, the mass was leached with considerable water, the resulting solution was concentrated to a strength of about 15 per cent hydrochloric acid, and the double salt of cesium antimony chloride was precipitated by the addition of antimony chloride. The precipitate so obtained was decomposed by boiling water and the filtered solution of the chlorides was then treated with ammonia and ammonium carbonate to remove aluminum, iron, antimony, and calcium impurities. The solution so obtained was acidified with hydrochloric acid, and the cesium values again precipitated in the form of the double cesium antimony chloride, thereby eliminating the bulk of the very troublesome ammonium salts. The double salt was again decomposed with boiling water, the filtered solution was evaporated to dryness, and the small amounts of ammonium salts present were volatilized by controlled heating. The crude chlorides were then dissolved in water, acidified, and the small amount of residual antimony was removed by the addition of hydrogen sulfide. The cesium chloride was next obtained in pure form by fractional crystallization from aqueous solution, the small amounts of lithium, sodium, potassium, and calcium impurities being thereby eliminated. A cesium chloride exceeding 99.9 per cent in purity was obtained by this procedure.

The cesium values can also be obtained from pollucite ore by treatment with 50 per cent sulfuric acid. The resulting mass is diluted with water and filtered at a temperature approximating 100°C. When this solution is cooled, the cesium values are directly obtained in the form of well-defined crystals of cesium alum, because in the first place the ore contains the cesium with enough aluminum present to form the alum and because the solubility of the cesium alum in the dilute acid solution diminishes markedly as the temperature is lowered from 100°C. to even 50°C. The amount of acid originally used and the extent of the subsequent dilution with water depend somewhat upon the quality of the ore at hand. The extent of the cooling of the filtered acid liquor and the possibility of need for further concentration to obtain one or more extra crops of alum are also dependent upon the grade of ore, since the fractionation of the various alums is altered by the presence of varying amounts of other salts. In any event, the cesium alum being most insoluble tends to crystallize out first and is followed in order of solubility by the alums of rubidium, potassium, and sodium. The cesium alum crystallizes in well-defined octahedral crystals, and like all the other members of the alum group contains twenty-four molecules of water of crystallization. The alum was early recognized as one of the compounds of cesium that offered opportunities for original work, as is evidenced by the studies of Redtenbacker in 1865, Setterberg (1881), Lock (1901), and Hart and Huseton (3) in 1914. Data concerning the solubility of cesium alum in water at various temperatures, as given in the literature, are rather confusing, owing probably to the use of material of varying purity. We have found that pure cesium alum ($Cs_2SO_4 \cdot Al_2(SO_4)_3 \cdot 24H_2O$) has a solubility of about 32 parts in 100 parts of water at 100°C., that at 50°C. the solubility drops to less than 1.5, and that at 5°C. only 0.25 part remains in 100 parts of water.

With cesium chloride as starting material, the nitrate and carbonate can be made according to the method of Wells as previously outlined. Cesium chromate can be made from the chloride by the use of pure silver chromate. Cesium sulfate, however, is not readily prepared in pure form from cesium chloride and an excess of sulfuric acid, on account of the marked stability of cesium acid sulfate at the fusion point. The usual procedure for eliminating small amounts of acid sulfate from the normal alkali sulfates is to fuse with small amounts of ammonium carbonate. Even when very large excesses of ammonium carbonate are used, the cesium sulfate still contains a small amount of the acid sulfate. This is readily removed by dissolving in water and adding cesium hydroxide to exact equivalence. The pure normal sulfate can then be crystallized from the aqueous solution.

Cesium alum is, in many cases, an ideal salt for preparing various salts of cesium. For example, cesium sulfate can be readily made by adding a hot solution of barium hydrate to a boiling solution of the cesium alum until all of the aluminum is precipitated. This point is very well indicated by spot-testing for alkalinity with bromothymol blue (pH 7.6). The filtered solution should give no test for either aluminum or barium, and pure cesium sulfate is then readily obtained by concentration. Cesium hydroxide can be prepared from a solution of the sulfate by the addition of a boiling solution of barium hydroxide to the point of exact equivalence. From the filtered cesium hydrate solution, the carbonate can be made by the introduction of carbon dioxide. In preparing cesium carbonate from the sulfate, experience in our laboratory shows that it is not good practice to add the barium hydroxide solution in excess, expecting to remove the excess barium later as barium carbonate along with the barium sulfate precipitate previously formed. Under these conditions the finished cesium carbonate solution will not be free of sulfates, in spite of the fact that such was the case previous to the introduction of the carbon dioxide.

Cesium, the most electropositive of all the elements, has a silvery white appearance when pure. It has a specific gravity of 1.9, melts at 28.5°C., and boils at 670°C. It ignites spontaneously in the air at room temperature, this action probably being due to the presence of traces of moisture. It also ignites spontaneously in *dry* oxygen at room temperature. In contact with traces of air left in highly evacuated glass tubes it gradually takes on a golden yellow color, and in the presence of more than minute traces of air it rapidly becomes black. When cooled to the temperature of carbon dioxide snow the metal is stable when exposed to air for short periods of time. The metal can be stored for long periods of time and its characteristic silvery appearance maintained by distilling it under a vacuum of 0.001 mm. of mercury into a glass apparatus consisting of two bulbs joined by a narrow open constriction. After the cesium has remained in one of the bulbs for several months under high vacuum and has scavenged the last traces of air from the glass interior, it is then distilled into the second bulb, and the first bulb is removed by means of a blowpipe. Metallic cesium reacts with water at ordinary temperature with explosive violence. In contact with ice, the metal generates hydrogen at all temperatures above −116°C.

Cesium metal can be prepared by the method of Erdmann and Kothmer, which consists in heating the hydroxide in an iron tube in an atmosphere of hydrogen with an excess of magnesium as the reducing agent. The method of Setterberg, by the electrolysis of the cyanide, produces a low yield which can be improved by using a mixture of 4 parts of cesium cyanide and 1 part of barium cyanide. In our opinion the metal can best be made by heating cesium chloride and metallic calcium in a nickel tube under a vacuum of 0.001 mm. to about 675°C. At this temperature the reaction ($2CsCl + Ca = 2Cs + CaCl_2$) takes place quietly and the metal can be distilled into a glass receiver. On redistillation under high vacuum the metal can be obtained in a high state of purity with a yield of 90 per cent.

Metallic cesium is used as such in the manufacture of photoelectric cells. However, in its use in radio and other low voltage tubes, where its function consists not only in scavenging the last traces of air left in the tube, but also in supplying positive ions at the surface of the filament, the metallic cesium is formed within the tube itself. This is done by loading so-called "getter" cups contained within the tube with different salts of cesium and various reducing agents. At the proper time the metal "getter" cup is heated by means of an induced current to the desired temperature for bringing about the reduction to metallic cesium. Cesium salts such as the chloride, carbonate, nitrate, and chromate mixed with various reducing agents such as magnesium, magnesium and graphite, barium–calcium alloy and others have been used with varying success, manufacturers keeping the details more or less secret.

In analyzing cesium-bearing silicates, such as pollucite and various micas, the alkalies can be obtained in the form of chlorides by the method of J. L. Smith. The perchlorate method leaves little to be desired in sharply separating the soluble perchlorates of lithium and sodium from the insoluble perchlorates of potassium, rubidium, and cesium. Since there are no truly specific reagents for potassium, rubidium, or cesium ions in the presence of one another the remainder of the problem is not so simple. In our experience, where cesium is the main constituent, the double precipitation of the double cesium antimony chloride coupled with spectroscopic examination by comparison with known mixtures gives good results.

From the foregoing description of the substantial cesium ore deposit uncovered in 1927 in South Dakota, it should be quite evident that during the past ten years there has been no shortage of cesium ore supplies. The demand, however, for finished cesium salts has been very limited, especially since 1929. Considerable research activities have been carried on by various concerns but to date, to the best of our knowledge, there has been no real commercial demand for cesium products. The small amounts required coupled with the exacting specifications for purity of products—some impurity limits being set as low as 0.001 per cent—have resulted in the price remaining high. With increased demand there is every reason to believe that present prices could be decreased very appreciably.

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SELENIUM OXYCHLORIDE AS A SOLVENT[1]

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I. INTRODUCTION

The concept of solvo-systems which Franklin (7, 8) applied with such spectacular success to liquid ammonia has been extended in somewhat modified forms in more recent years to a number of other solvents. Among these researches the following studies of solvents have peculiar significance in connection with this paper: (*1*) acetic acid by Davidson and his coworkers (2, 3, 4, 5), (*2*) hydrogen sulfide by Wilkinson and Quam (27, 28, 33), (*3*) sulfuric acid by Kendall, Davidson, and others (19, 20), (*4*) hydroxylamine by Audrieth (1), (*5*) phosgene by Germann (10, 11), and (*6*) sulfur dioxide by Jander and his coworkers (13, 14, 15, 16, 17). The most recently reported studies are of especial interest to the author, since Jander's views are so closely in accord with those expressed in this paper.

It will be recognized, therefore, that there is gradually being accumulated a body of facts from which general similarities of behavior may be recognized. Kahlenberg's view that a solution is "a chemical compound which does not obey the law of definite proportions" is a qualitative one, but it provides a basis for rational chemical approach to the problem. There can be, from the broad point of view of a modern inorganic chemist, no serious question that when a solute dissolves in a solvent a chemical change occurs. (The ideal solution is analogous to the ideal gas.) The nature of this chemical change is intimately related in many instances at least to the tendency of the solute to act either as an electron pair donor or as an electron pair acceptor toward the solvent. If the solvent is polar the formation of complex ions may be expected. Many "definitions" of acid have been proposed. The Brønsted statement has been the one most generally accepted in the last few years, but it is by no means of "universal" application. The author proposes the following as useful and rational broad definitions for the terms "acid" and "base": *A solute is an acid when its molecule (neutral or charged) is an electron pair acceptor toward the molecule or an ion of the solvent;* on the other hand, *a solute is a base when its molecule (neutral or charged) is an electron pair donor toward the molecule or an ion of the solvent.* These statements are similar to the Brønsted statement but they are more universal, since they permit application to solvents other than "hydrogen" solvents.

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[1] This paper is respectfully dedicated by the author to the late Professors Victor Lenher and Edward Curtis Franklin in appreciation of the continuing inspiration of their extensive and classical work in the fields reviewed here. It was presented at the Second Annual Symposium of the Division of Physical and Inorganic Chemistry of the American Chemical Society, held at Cleveland, Ohio, December 27–29, 1937.

The fundamental concept which is expressed in the above definitions was stated very clearly and concisely by Gilbert N. Lewis (24) in 1923 in his monograph on "Valence and the Structure of Atoms and Molecules."

> "We are inclined to think of substances as possessing acid or basic properties, without having a particular solvent in mind. It seems to me that with complete generality we may say that a basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom, and that an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond, the acid substances accept such a pair."

Walden (31) gives an excellent review of acid–base concepts and points out that the Lewis views have not been accepted generally because classical dissociation constants "become meaningless" and other acid–base characteristics appear to be "purely incidental observations." The author, however, believes that the Lewis view is useful in working in the field of non-aqueous solutions (particularly in non-hydrogen solutions) and he also believes that the use of such a term as "pseudo-acid" is unnecessary.

This paper will outline the selenium oxychloro solvo-system of compounds. The unusual interest in the classical investigations on selenium oxychloride by Lenher (18, 22, 26, 29) and his coworkers at the University of Wisconsin was due to the demonstrated reactivity of this compound toward very many substances. Thus most of the published papers on selenium oxychloride deal with the substance as a reagent rather than as a solvent as this term is usually understood.

Selenium oxychloride has a dielectric constant which approaches the same order of magnitude as the dielectric constant of water.[2] The high conductance, 2×10^{-5} mhos (18), indicates that the ion concentration of the pure liquid is relatively very high. In this respect it is similar to sulfuric acid, and this property is probably related to the fact that these solvents are powerful solvolyzing agents.

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[2] Wildish measured the dielectric constant and reports 46 at 20°C. (32). This higher value is the result obtained from some preliminary observations made by Dr. Eric Ackerland in the Research Laboratory of Electrical Engineering of the Polytechnic Institute of Brooklyn.

II. IONIZATION

In table 1 the ionization of selenium oxychloride is postulated. This ionization is similar to the ionization of other typical solvents, as becomes apparent when we compare these several equations. This postulation for the ionization (autoionization) of selenium oxychloride is based upon the following evidence: (*a*) the conductance of the pure liquid, (*b*) the products formed when solutions are subjected to electrolysis, (*c*) the products formed when a metal reacts with selenium oxychloride, (*d*) the composition of solvates of selenium oxychloride, such as stannic chloride disolvate and pyridine monosolvate, and (*e*) the metathetical reactions which have been carried out in selenium oxychloride solutions. It is admitted that this evidence is all indirect. This is true likewise of all evidence in support of postulations regarding ionization.

TABLE 1

Ionization of various solvents

$$\begin{aligned}
2\mathrm{SeOCl_2} &\rightleftharpoons (\mathrm{SeOCl\cdot SeOCl_2})^+ + \mathrm{Cl}^- \\
2\mathrm{H_2O} &\rightleftharpoons (\mathrm{H_3O})^+ + (\mathrm{OH})^- \\
2\mathrm{NH_3} &\rightleftharpoons (\mathrm{NH_4})^+ + (\mathrm{NH_2})^- \\
2\mathrm{HC_2H_3O_2} &\rightleftharpoons (\mathrm{H_2C_2H_3O_2})^+ + (\mathrm{C_2H_3O_2})^- \\
2\mathrm{H_2SO_4} &\rightleftharpoons (\mathrm{H_3SO_4})^+ + (\mathrm{HSO_4})^- \\
2\mathrm{COCl_2} &\rightleftharpoons (\mathrm{COCl\cdot COCl_2})^+ + \mathrm{Cl}^{-*} \\
\text{or } \mathrm{COCl_2} &\rightleftharpoons (\mathrm{CO})^{++} + 2\mathrm{Cl}^- \qquad \text{(Germann)} \\
2\mathrm{SO_2} &\rightleftharpoons (\mathrm{SO})^{++} + (\mathrm{SO_3})^{--} \qquad \text{(Jander)} \\
\text{or } 4\mathrm{SO_2} &\rightleftharpoons (\mathrm{SO\cdot 2SO_2})^{++} + (\mathrm{SO_3})^{--\dagger}
\end{aligned}$$

* The author believes that primary rather than secondary ionization predominates, and the probable electronic configuration suggests solvation of the cation.

† Solvation of the doubly charged cation SO^{++} follows quite logically from a consideration of the probable electronic structure.

III. ELECTROLYSIS

The conductance of selenium oxychloride is so low that it is not convenient to electrolyze the pure liquid. However, electrolytic decomposition of the substance does yield chlorine at the anode, and the liquid around the cathode becomes reddish brown, which indicates that selenium monochloride is formed.

A solution of potassium chloride (saturated at room temperature) (30) was electrolyzed for 90 min. Chlorine was liberated at the anode, and selenium dioxide was precipitated in the neighborhood of the cathode.

The solution around the cathode became red brown in color, and when a portion was treated with water elementary selenium was deposited.

A solution of stannic chloride in selenium oxychloride when subjected to electrolytic decomposition likewise yielded chlorine at the anode and selenium dioxide and selenium monochloride at the cathode. Accordingly we may formulate the equation for the electrolytic decomposition of selenium oxychloride as follows:

$$\text{anodic} \qquad 2\,Cl^- - 2\ominus \rightarrow Cl_2$$

$$\text{cathodic} \qquad 6(SeOCl)^+ + 6\ominus \rightarrow 6SeOCl$$

$$6SeOCl \rightarrow 2SeO_2 + Se_2Cl_2 + 2SeOCl_2$$

In table 2 these reactions are compared with those of water, ammonia, and phosgene.

TABLE 2

Comparison of electrolysis of water, ammonia, phosgene, and selenium oxychloride

	CATHODIC REACTION	ANODIC REACTION
Water.....	$2(H_3O)^+ + 2\ominus \rightarrow H_2 + 2H_2O$	$4(OH)^- - 4\ominus \rightarrow 2H_2O + O_2$
Ammonia..	$2(NH_4)^+ + 2\ominus \rightarrow H_2 + 2NH_3$	$6(NH_2)^- - 6\ominus \rightarrow 4NH_3 + N_2$
Phosgene..	$2(COCl\cdot COCl_2)^+ + 2\ominus \rightarrow CO + 3COCl_2$	$2Cl^- - 2\ominus \rightarrow Cl_2$
Selenium oxychloride.	$6(SeOCl\cdot SeOCl_2)^+ + 6\ominus \rightarrow 2SeO_2 + Se_2Cl_2 + 2SeOCl_2$	$2Cl^- - 2\ominus \rightarrow Cl_2$

IV. ACTION ON METALS

The action of selenium oxychloride on several metals has been studied by W. L. Ray (29). Copper, lead, cobalt, nickel, iron, tin, and silver yield the chlorides of the metals, selenium dioxide, and selenium monochloride. Ray formulated the reaction of copper and selenium oxychloride as follows:

$$3Cu + 4SeOCl_2 \rightarrow 3CuCl_2 + Se_2Cl_2 + 2SeO_2$$

Ray's analytical data may be explained by the following formulation, which is in accordance with the electrolytic decomposition:

$$3Cu + 6SeOCl^+ \rightarrow 3Cu^{++} + Se_2Cl_2 + SeO_2 + 2SeOCl_2$$

$$3Cu^{++} + 6Cl^- \rightarrow 3CuCl_2$$

This action with copper demonstrates that the selenium oxychloro ion is a powerful oxidizing agent, and this fact accounts in part at least for the reactivity of selenium oxychloride. (For comparison see table 3.)

Erickson (6) compared qualitatively the action of selenium oxychloride and the action of a 20 per cent solution of stannic chloride in selenium oxychloride on the following metals: magnesium, calcium, lead, mercury, copper, zinc, and sodium. It was observed that in general the metals are more reactive and more soluble in the solution of stannic chloride than in selenium oxychloride alone. These observations are analogous to those of Germann (10) on the action of a solution of aluminum chloride in phosgene on metals as compared with the action of phosgene alone. Stannic chloride is to be regarded as an acid of the selenium oxychloro system.

Another series of experiments showed that the solubilities of barium chloride, calcium chloride, and potassium chloride were greater in a solution of stannic chloride in selenium oxychloride than in selenium oxychloride alone (*vide infra*).

TABLE 3

Comparison of action of metals on water, ammonia, phosgene, and selenium oxychloride

SOLVENT	REACTION
Water	$2M' + 2H_3O^+ \rightarrow H_2 + 2M^+ + 2H_2O$
Ammonia	$2M' + 2NH_4^+ \rightarrow H_2 + 2M^+ + 2NH_3$
Phosgene	$2M' + 2COCl\cdot COCl_2^+ \rightarrow CO + 2M^+ + 2COCl_2$
Selenium oxychloride	$6M' + 6SeOCl\cdot SeOCl_2^+ \rightarrow 2SeO_2 + Se_2Cl_2 + 6M^+ + 8SeOCl_2$

TABLE 4

Disolvates formed from selenium oxychloride and certain chlorides

ANALYTICAL FORMULAS	RATIONAL FORMULAS
$TiCl_4\cdot 2SeOCl_2$	$(SeOCl)_2^{++}\ TiCl_6^{--}$
$SnCl_4\cdot 2SeOCl_2$	$(SeOCl)_2^{++}\ SnCl_6^{--}$
$SiCl_4\cdot 2SeOCl_2$	$(SeOCl)_2^{++}\ SiCl_6^{--}$
$FeCl_3\cdot 2SeOCl_2$	$(SeOCl)_2^{++}\ FeCl_5^{--}$

V. ELECTRON PAIR ACCEPTORS (ACIDS)

In selenium oxychloride, chlorides of non-metals or of amphoteric elements are to be regarded as acids. Several chlorides which are soluble in selenium oxychloride separate from supersaturated solutions as solvates (34). Titanium tetrachloride, tin tetrachloride, silicon tetrachloride, and ferric chloride all form disolvates. If these substances are formulated in accordance with the usual ionic forms we find that this formulation is consistent with the postulation regarding the autoionization of the parent solvent (see table 4). Many oxides are solvolyzed by selenium oxychloride, but several appear to dissolve. Lenher (22) demonstrated the powerful solvent action of a solution of sulfur trioxide in selenium oxychloride. It is evident from our studies that this solution is a chlorosulfonic acid of the selenium oxychloro system $(SeOCl)(SO_3Cl)$. Molybdic oxide likewise appears as an acid when dissolved in selenium oxychloride:

$$(SeOCl)(MoO_3Cl) \text{ or } (SeOCl)_2(MoO_3Cl_2)$$

Stannic chloride acts as an electron pair acceptor toward chloride ions as follows:

$$SnCl_4 + 2Cl^- \rightarrow SnCl_6^{--}$$

and sulfur trioxide behaves in a similar manner:

$$SO_3 + Cl^- \rightarrow SO_3Cl^-$$

Chemists have been familiar with these ions for a long time.

Arsenic trichloride dissolves to an unlimited extent in selenium oxychloride, and the behavior of this solution is typical of an acid of this system, $(SeOCl)AsCl_4$. No solid phases have been observed.

VI. ELECTRON PAIR DONORS (BASES)

Ammonia and selenium oxychloride

Ammonia is regarded as a typical base. The reaction of ammonia with water is formulated as

$$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$$

The primary reaction between ammonia and selenium oxychloride is regarded by us to be entirely analogous, as

$$NH_3 + SeOCl_2 \rightarrow NH_3SeOCl^+ + Cl^-$$

This material has only a limited solubility. When ammonia is passed into selenium oxychloride white platelets separate. However, this material undergoes progressive decomposition and its exact composition has not been established. The reaction was studied by allowing standard solutions of ammonia and of selenium oxychloride in carbon tetrachloride to react and, after separating the solid, the solution was analyzed for chlorine, ammonia, and selenium. These results indicated that the monoammonate was formed as a solid phase when less than 1 mole of ammonia was used. If more than 1 mole of ammonia was used a higher ammonate was also formed (23). Substituted ammonias which have been studied, with the exception of pyridine and quinoline, appear to undergo immediate solvolysis.

Pyridine and selenium oxychloride

Pyridine reacts with selenium oxychloride to form a monosolvate.[3] Selenium oxychloride (8.3 g.) was dissolved in 50 ml. of carbon tetrachloride and pyridine (3.9 g.) was dissolved in 50 ml. of carbon tetrachloride. The two solutions were added dropwise to 50 ml. of carbon tetrachloride cooled in an ice bath, while the reaction mixture was stirred. A white solid separated immediately. This solid was separated by filtration, and washed with carbon tetrachloride. Two portions were then taken. The first portion was dissolved in water and diluted to 1 liter, and this solution was analyzed for chloride ion, selenium, and pyridine. The second portion was placed in an Abderhalden oven and heated at 61°C. ($CHCl_3$) for 5 hr. The material was allowed to cool; a sample was weighed and analyzed for chloride ion, selenium, and pyridine. A second sample was prepared in the same manner, except that the solid was dried for a period of 21 hr. Analytical data are given in table 5. These facts prove that pyridine forms a simple "addition" compound with selenium oxychloride.

TABLE 5

Analytical data for the reaction product of selenium oxychloride and pyridine

SAMPLE	DATA			
Sample A: material moist with CCl_4:				
Se	0.0794	0.0774	0.0787	0.0768
AgCl	0.2811	0.2823	0.2818	0.2804
ml. of 0.1503 *N* NaOH	6.5	6.9	7.1	6.6
Average ratio Se:Cl:C_5H_5N	1:1.986:1.027			
	Se	Cl	C_5H_5N	
Sample A: material dried at 61°C. *in vacuo* (7 hr.):				
Calculated for $SeOCl_2 \cdot C_5H_5N$	32.24	28.96	32.31	
Found	31.60 31.70	28.24 28.24	31.11 30.70	
Sample B: material dried at 61°C. *in vacuo* (21 hr.):				
Found	31.81 31.81	28.61 28.56	32.97 31.57 32.41 33.46	

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[3] Studies on the reaction between selenium oxychloride and pyridine are now being carried on by Julius Jackson in this laboratory.

When taken in conjunction with the reactions of pyridine with stannic chloride, ferric chloride, etc., described in the next section of this paper they indicate conclusively that pyridine is an electron pair donor (base) toward selenium oxychloride. This reaction may be formulated as follows:

$$C_5H_5N + SeOCl_2 \rightarrow (C_5H_5N\ SeOCl)^+\ Cl^-$$

Quinoline and selenium oxychloride

Quinoline reacts with selenium oxychloride in a manner quite similar to that in which pyridine reacts. An addition compound is formed which may be explained by the following equation:

$$C_9H_7N + SeOCl_2 \rightarrow (C_9H_7N\ SeOCl)^+\ Cl^-$$

Therefore quinoline may be regarded as a base, because it is an electron pair donor toward the selenium oxychloro ion.

Water and selenium oxychloride

The Ditte compound $SeO_2 \cdot 2HCl$ is to be regarded either as a hydrate of selenium oxychloride ($H_2OSeOCl^+\ Cl^-$) or as dichloroselenious acid, ($H_2SeO_2Cl_2$). When water is dissolved in selenium oxychloride it acts as an electron pair donor toward the solvent and the increased conductance of the solution is due to the presence of $H_2OSeOCl^+$ ions and chloride ions. Labile protons account for the thermal decomposition of $SeO_2 \cdot 2HCl$, and these reactions may be formulated as follows:

$$H_2O \cdot SeOCl \cdot Cl \rightleftharpoons H_2SeO_2Cl_2$$

$$H_2SeO_2Cl_2 \rightarrow 2HCl + SeO_2$$

$$H_2O \cdot SeOCl \cdot Cl \rightarrow H_2O + SeOCl_2 \qquad (12)$$

These characteristics of selenium oxychloride and water will be made the subject of a future communication.

Salts of strong metals and selenium oxychloride

Hydroxides of the alkali and alkaline earth metals are usually regarded as typical bases. On the basis of the definition which has been proposed sodium hydroxide is a salt which quite incidentally acts as a base in aquo solution. The molecule which is an electron pair donor is the charged molecule (the hydroxide ion). In an exactly analogous manner chlorides of the alkali and alkaline earth metals function as bases in selenium oxychloride, and the molecule which is an electron pair donor is the charged molecule (the chloride ion).

VII. REACTIONS IN SELENIUM OXYCHLORIDE SOLUTIONS

Calcium chloride and stannic chloride (precipitation)

Anhydrous calcium chloride was dissolved in a hot solution of stannic chloride in selenium oxychloride. When the solution was cooled crystals separated from it (6). These crystals were removed by filtration and washed with chloroform; the moist material was analyzed for tin, calcium, chloride ion, and selenium. Four samples were prepared; the details of their preparation are given in table 6. The atomic ratios were computed from the analytical data and are given in table 7. While these results do not show that a pure substance is formed, they do indicate that calcium chloride reacts with stannic chloride. The solid phase is probably a mixture of two or more of the possible calcium chlorostannates. Potassium chloride forms a precipitate with stannic chloride. This precipitate contains chlorine, potassium, and tin, but it has not been examined quantitatively. Other solid phases have been observed, also, and studies of these phases are projected.

TABLE 6

Preparation of samples

SAMPLE NO.	$SnCl_4$	$CaCl_2$ TAKEN	$SeOCl_2$ TAKEN
	grams	*grams*	*grams*
1	3.4	0.3	12.2
2	3.4	0.4	12.2
3	2.28	0.4	12.2
4	5.7	0.4	12.2

TABLE 7

Atomic ratios computed from the analytical data

SAMPLE NO.	TIN	CHLORINE	CALCIUM	SELENIUM
1	1.00	10.76	0.72	2.97
2	1.00	9.39	0.56	3.13
3	1.00	14.59	0.75	2.79
4	1.00	14.06	0.81	3.07
Calculated for $CaSnCl_6 \cdot 3SeOCl_2$....	1.00	12.00	1.00	3.00

Conductance titrations

The conductance method has been employed to follow the course of reactions between substances dissolved in selenium oxychloride. Definite breaks in titration curves indicate that chemical changes occur. Seven typical titrations will be described.

Apparatus. The conductivity measurements were made employing a circuit similar to that used by Garman and Kinney (9). A glass conductivity cell with sealed-in platinum electrodes was used. The cover of the cell was of ground glass, and a stirrer and the tip of a buret were admitted through openings in the cover. A special 15-ml. buret graduated in 1/20 ml. was used. The buret was fitted with a ground-glass stopper, and a groove in the stopper could be made to correspond with a groove in the buret so that a small air passage was formed. Volumetric flasks of 10- and 15-ml. capacity were used for preparing standard solutions.

TABLE 8

*Experimental details of conductance titrations**

SYSTEM	BASE		ACID		TITRATION REAGENT	STOICHIOMETRICAL RATIOS INDICATED
	Weight	Volume of solution	Weight	Volume of solution		
	grams	*ml.*	*grams*	*ml.*		
C_5H_5N-$SnCl_4$..........	0.2043	12	1.3267	10	Acid	$2C_5H_5N$, $1SnCl_4$
C_5H_5N-$SnCl_4$..........	0.5000	13.5	0.3090	9	Base	$1C_5H_5N$, $2SnCl_4$ $1C_5H_5N$, $1SnCl_4$ $2C_5H_5N$, $1SnCl_4$ $3C_5H_5N$, $1SnCl_4$
KCl-$SnCl_4$.............	0.0912	12	0.9209	10	Acid	$1KCl$, $2SnCl_4$ $1KCl$, $1SnCl_4$
$CaCl_2$-$SnCl_4$...........	0.2881	15	0.2131	12	Base	$1CaCl_2$, $2SnCl_4$ $1CaCl_2$, $1SnCl_4$ $3CaCl_2$, $2SnCl_4$
C_5H_5N-$FeCl_3$..........	0.8173	14	0.3013	11	Base	$1C_5H_5N$, $1FeCl_3$ $2C_5H_5N$, $1FeCl_3$ $3C_5H_5N$, $1FeCl_3$
C_5H_5N-SO_2............	0.4652	10	0.0971	12	Base	$1C_5H_5N$, $1SO_2$ $2C_5H_5N$, $1SO_2$
C_5H_5N-$AsCl_3$..........	0.3237	15	0.1963	12	Base	$1C_5H_5N$, $2AsCl_3$ $1C_5H_5N$, $1AsCl_3$ $2C_5H_5N$, $1AsCl_3$

* These data are from experimental studies made by Mr. Alvin Gordon. The author is pleased to acknowledge the assistance of Dr. Eric Ackerland, who helped in assembling the equipment. Mr. Lankau (21) and Mr. McGhie (25) had previously made numerous titrations using the familiar Kohlrausch equipment.

Procedure. Approximately 4 ml. of selenium oxychloride was placed in a tared 10- or 15-ml. volumetric flask, and the anhydrous chloride was added. The flask and contents were again weighed. When the anhydrous chloride had dissolved the solution was diluted to 10 or 15 ml. This solution, which was the titrating reagent, was transferred to the 15-ml. buret.

The solution to be titrated was prepared as follows: Approximately 4 ml. of selenium oxychloride was weighed in a tared weighing bottle, the anhydrous chloride was added, and the weighing bottle and contents were reweighed. The solution was transferred quantitatively to the conductivity cell. Additional selenium oxychloride was added in sufficient amounts to cover the platinum electrodes. The cell was placed in an oil bath, and the stirrer and buret were placed in position. The conductance of the solution was measured. Successive portions of the solution were then added from the buret, and the conductivities were measured after each addition. Typical data are presented graphically in figures 1 to 7. We will now take up a brief discussion of each system. Table 8 gives certain experimental details.

Pyridine and stannic chloride

A solution of pyridine in selenium oxychloride is an excellent conductor. The ions present to which we may attribute this conductance are probably the selenium oxychloropyridinium ions and the chloride ions. Curve 1 in figure 1 presents the data obtained when a solution of pyridine in selenium oxychloride was titrated with a solution of stannic chloride in selenium oxychloride. A single inflection in this curve occurs at the point where there were present in the solution approximately 2 moles of pyridine to 1 mole of stannic chloride. This may be attributed to the formation of secondary selenium oxychloropyridinium hexachlorostannate, and the equation for the molecular reaction may be formulated as follows:

$$2(C_5H_5NSeOCl)Cl + (SeOCl)_2(SnCl_6) \rightarrow (C_5H_5NSeOCl)_2(SnCl_6) + 2SeOCl_2$$

It is evident that the solution of pyridine is ionized to a marked degree and so the ionic reaction may be formulated as follows:

$$2(C_5H_5NSeOCl)^+ + 2Cl^- + (SeOCl)_2(SnCl_6) \rightarrow 2(C_5H_5NSeOCl)^+ + (SnCl_6)^{--} + 2SeOCl_2$$

or perhaps merely as follows:

$$2Cl^- + (SeOCl)_2(SnCl_6) \rightarrow (SnCl_6)^{--} + 2SeOCl_2$$

The decrease in conductance is attributed in part to dilution of the solution (since stannic chloride is a poorer conductor than pyridine), but more particularly to the replacement of chloride ion by hexachlorostannate ions.

Solutions of the same substances were employed in obtaining the data presented in figure 2. However, in this instance the reagent was the solution of pyridine and the conductance of the solution of stannic chloride was increased by the addition of the reagent. Concentrations of reactants were higher, and four inflections in the curve may be recognized. The following equations are presented to explain the experimental observations:

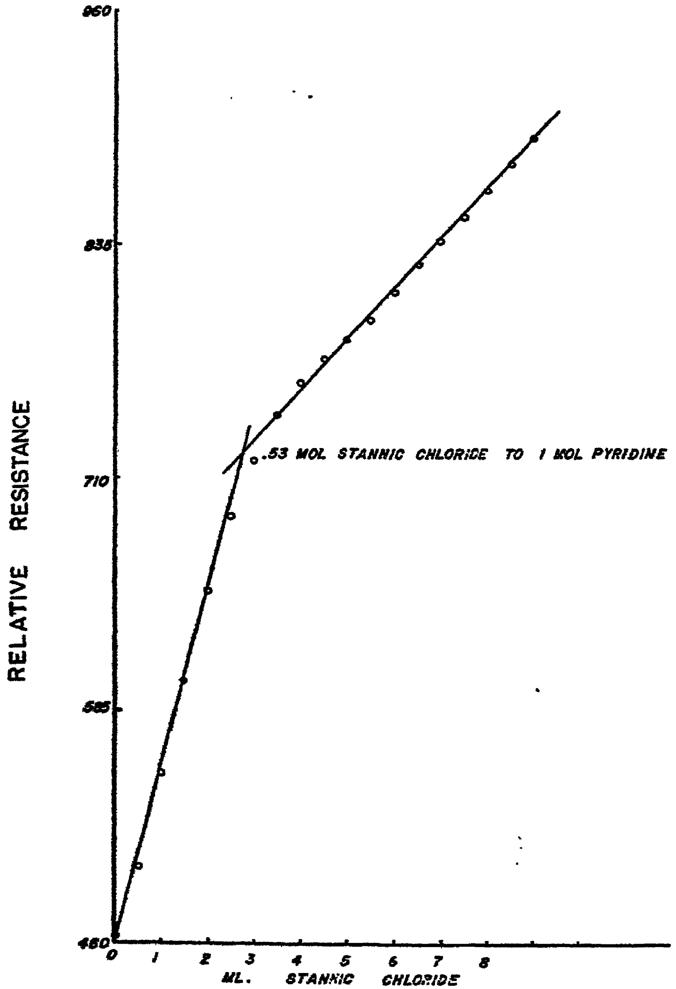

Fig. 1. Conductance titration of a solution of pyridine in selenium oxychloride with a solution of stannic chloride in selenium oxychloride.

$$2(SeOCl)_2SnCl_6 + C_5H_5NSeOCl^+ + Cl^- \rightarrow (C_5H_5NSeOCl)^+ + (SeOCl)_3(SnCl_6)_2^- + SeOCl_2$$

$$(SeOCl)_2SnCl_6 + C_5H_5NSeOCl^+ + Cl^- \rightarrow (C_5H_5NSeOCl)^+ + (SeOCl)SnCl_6^- + SeOCl_2$$

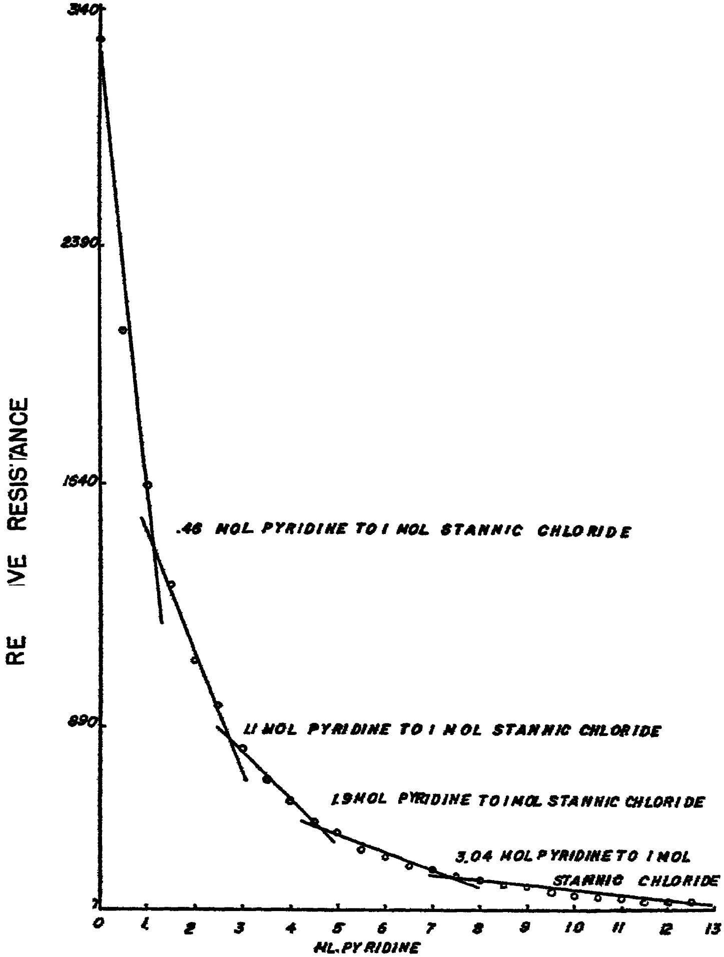

FIG. 2. Conductance titration of a solution of stannic chloride in selenium oxychloride with a solution of pyridine in selenium oxychloride.

$$(SeOCl)_2SnCl_6 + 2C_5H_5NSeOCl^+ + 2Cl^- \rightarrow 2(C_5H_5NSeOCl)^+ + SnCl_6^{--} + 2SeOCl_2$$

$$(SeOCl)_3SnCl_7 + 3C_5H_5NSeOCl^+ + 3Cl^- \rightarrow 3(C_5H_5NSeOCl)^+ + SnCl_7^{---} + 3SeOCl_2$$

The first equation postulates a hypothetical salt of the formula

$$(C_5H_5NSeOCl)(SeOCl)_3(SnCl_6)_2$$

which might be analogous to potassium tetraoxalate, $KH_3(C_2O_4)_2$. The second equation postulates a hypothetical primary salt of the formula

$$(C_5H_5NSeOCl)(SeOCl)(SnCl_6)$$

and the third equation gives the secondary salt postulated to explain

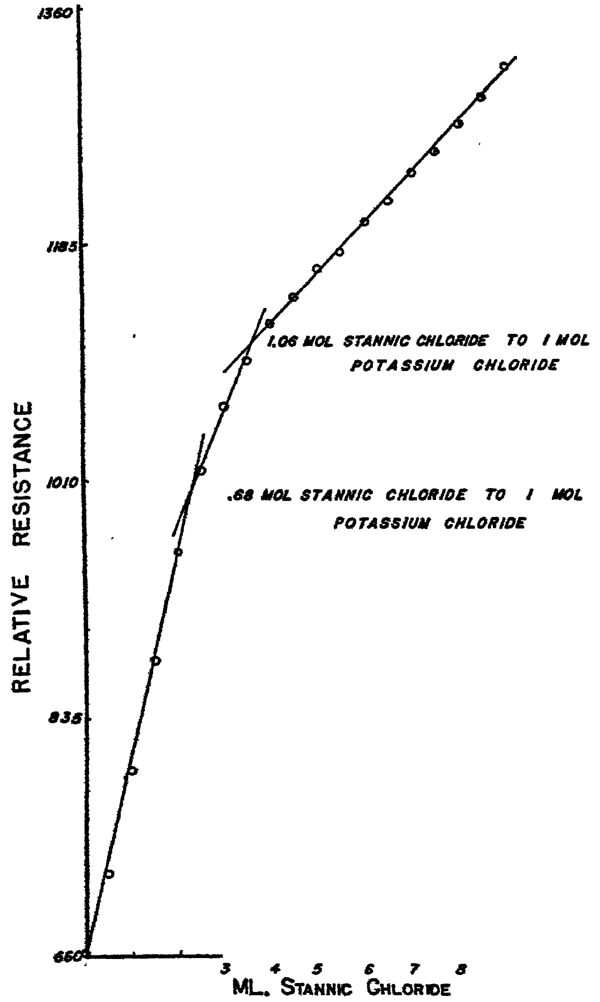

FIG. 3. Conductance titration of a solution of potassium chloride in selenium oxychloride with a solution of stannic chloride in selenium oxychloride.

curve 1. The fourth equation assumes the existence of a chlorostannate ion with a coördination number of seven, which may be possible but certainly is not usual. The author freely admits that these postulations are speculative, but their validity may be proved by future experimental work. On the other hand, future experiments will probably lead to modifications of these postulations. It should be remembered that association

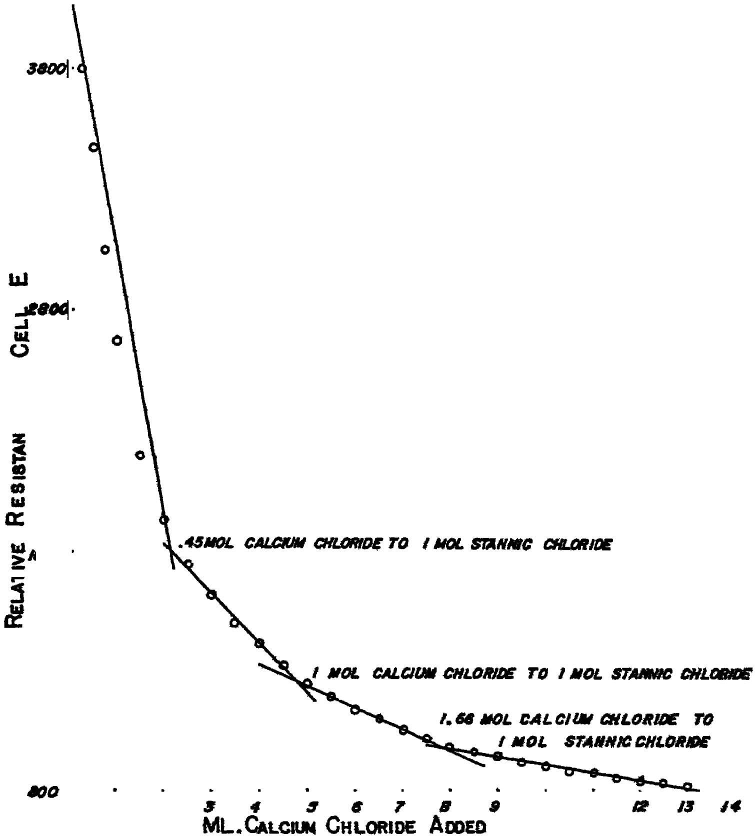

FIG. 4. Conductance titration of a solution of stannic chloride in selenium oxychloride with a solution of calcium chloride in selenium oxychloride.

of ions is considered as probable in concentrated solutions, and here it is suggested that such association follows rather simple stoichiometrical ratios.

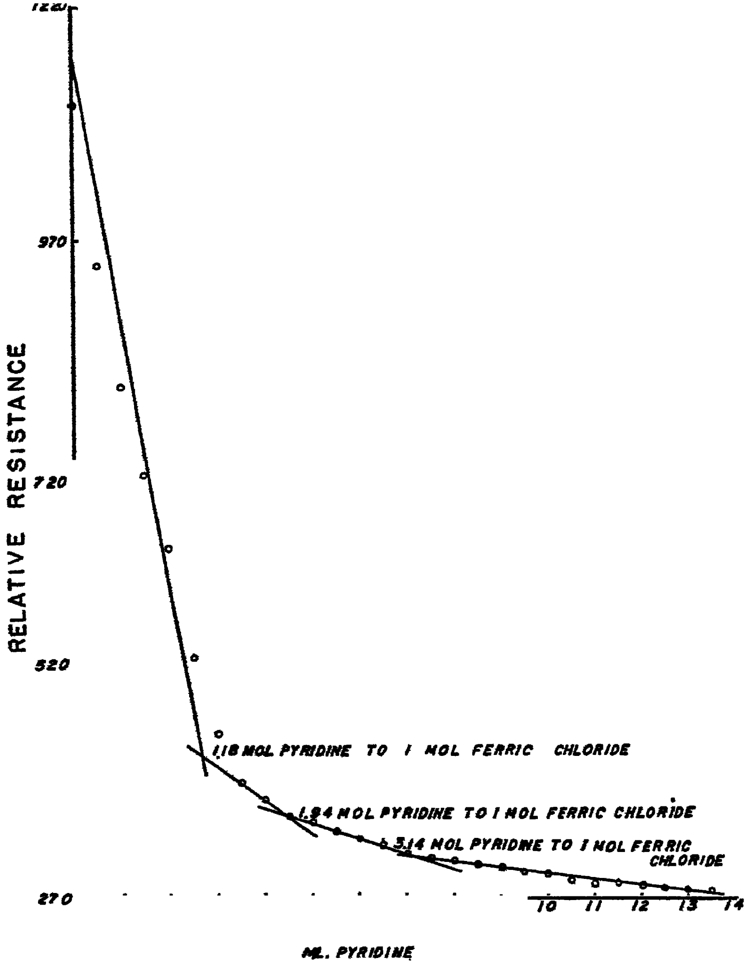

FIG. 5. Conductance titration of a solution of ferric chloride in selenium oxychloride with a solution of pyridine in selenium oxychloride.

Potassium chloride and stannic chloride

The conductance of a solution of potassium chloride in selenium oxychloride is decreased by the addition of a solution of stannic chloride. In the curve of figure 3 two inflections may be observed; these are explained on the assumption that solutions of salts of the following formulas are present at these inflection points:

$$K(SeOCl)_3(SnCl_6)_2 \text{ and } K(SeOCl)(SnCl_6)$$

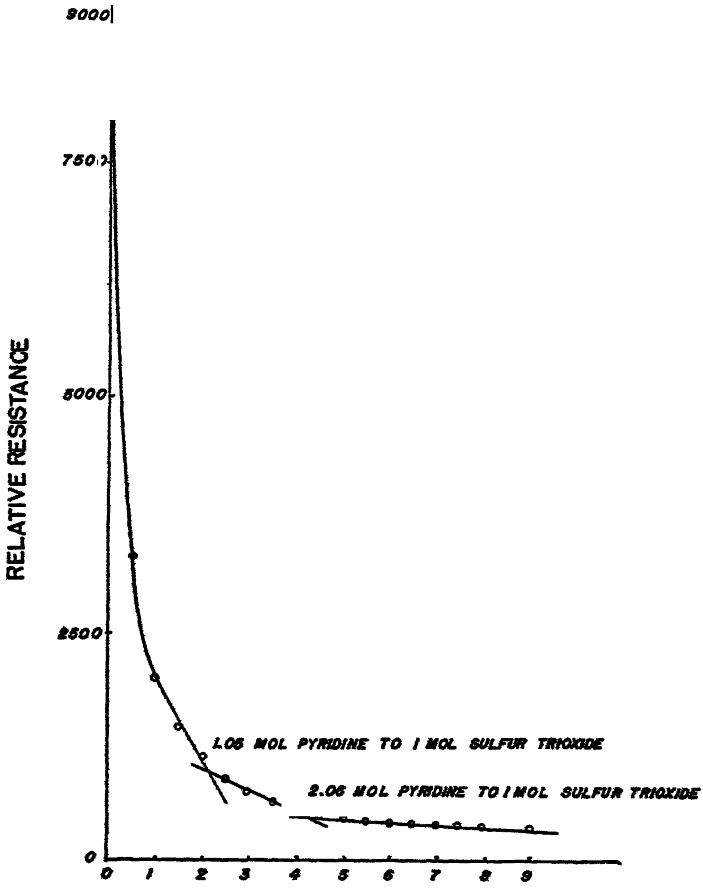

FIG. 6. Conductance titration of a solution of sulfur trioxide in selenium oxychloride with a solution of pyridine in selenium oxychloride.

It will be noted that these salts are analogous to the first two pyridinium salts postulated from the data presented in figure 2.

Calcium chloride and stannic chloride

The conductance of a solution of stannic chloride in selenium oxychloride is increased by the addition of a solution of calcium chloride, and the form of the curve in figure 4 is very similar to the curve of figure 2. The formulas of the salts which may exist at the three inflection points of curve 4 may be written as follows:

$$Ca[(SeOCl)SnCl_6]_2, CaSnCl_6, \text{ and } Ca_3(SnCl_7)_2$$

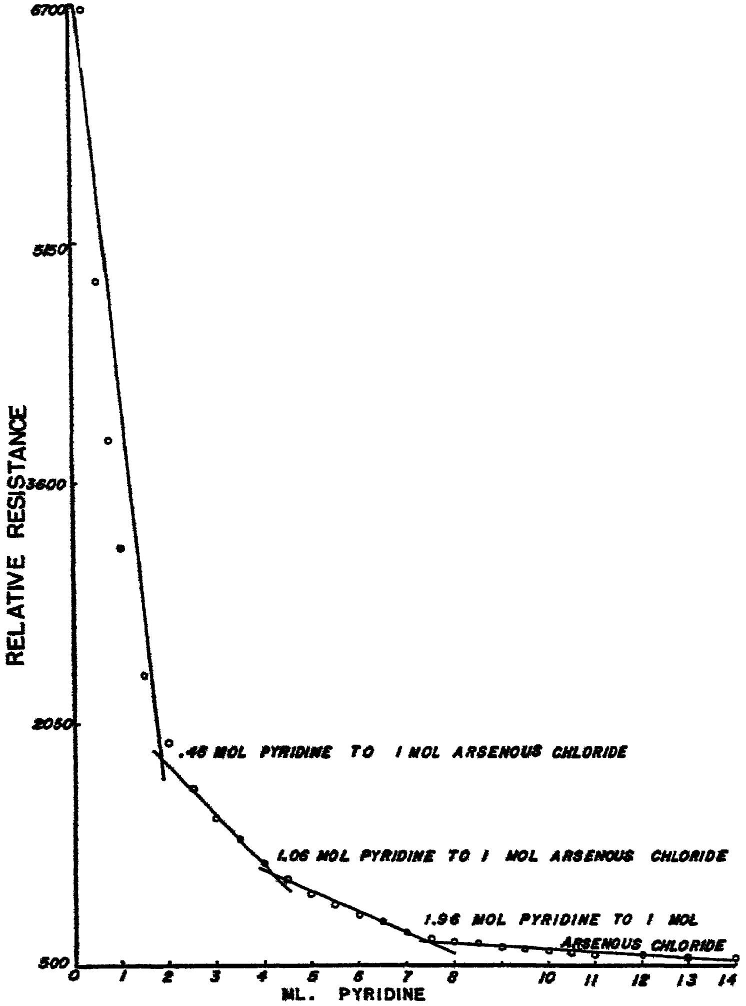

FIG. 7. Conductance titration of a solution of arsenic trichloride in selenium oxychloride with a solution of pyridine in selenium oxychloride.

and it is to be noted that these are analogous to the last three pyridinium salts postulated for figure 2.

Pyridine and ferric chloride

Ferric chloride dissolved in selenium oxychloride is a moderately good conductor, but the conductance is increased by the addition of pyridine. The curve in figure 5 indicates three inflections corresponding to the formation of primary, secondary, and tertiary salts. These may be formulated as:

$$(C_5H_5NSeOCl)(SeOClFeCl_5),\ (C_5H_5NSeOCl)_2(FeCl_5),\ \text{and}\ (C_5H_5NSeOCl)_3(FeCl_6)$$

A usual coördination number for iron is five and of course six occurs frequently. A solution of ferric chloride in selenium oxychloride is ruby-red in color. This color is practically identical with a solution of potassium pentachloroferrite in an aqueous solution. It will be recalled that the crystals of potassium pentachloroferrite are likewise of a ruby-red color.

Pyridine and sulfur trioxide

The curve in figure 6 presents the data obtained when a solution of sulfur trioxide is titrated with a solution of pyridine. Two inflections are indicated, and there may possibly be a third which we will neglect here. The salts formed may be written as

$$(C_5H_5NSeOCl)SO_3Cl\ \text{and}\ (C_5H_5NSeOCl)_2SO_3Cl_2$$

Titrations at higher dilutions indicate a single inflection at the point corresponding to the formation of the primary salt.

Pyridine and arsenic trichloride

Wise (34) has shown that arsenic trichloride mixes with selenium oxychloride in all proportions. Since arsenic is a typical non-metal, we would expect arsenic trichloride to act as an acid in selenium oxychloride. The validity of this prediction is demonstrated by the results which are presented graphically in the curve of figure 7. The three inflection points indicate salts which may be formulated as:

$$(C_5H_5NSeOCl)(SeOCl)(AsCl_4)_2,\ (C_5H_5NSeOCl)(AsCl_4),\ \text{and}\ (C_5H_5NSeOCl)_2(AsCl_5)$$

VIII. SUMMARY

1. This paper presents experimental evidence to support the thesis that selenium oxychloride is a parent solvent of a system of compounds in the Franklin–Germann sense (acids, bases, and salts). The known facts regarding selenium oxychloride as a solvent are correlated on this basis.

2. It is proposed to use the following broad definitions for the terms

"acid" and "base": *A solute is an acid when its molecule (neutral or charged) is an electron pair acceptor toward the molecule or an ion of the solvent; a solute is a base when its molecule (neutral or charged) is an electron pair donor toward the molecule or an ion of the solvent.* These statements are sufficiently broad to permit application to parent solvents such as phosgene, sulfur dioxide, and selenium oxychloride, as well as the ordinary solvents which ionize to give the solvated proton. These statements are proposed as merely extensions of the Brønsted definition and the latter should be retained ordinarily.

3. Metathetical reactions (essentially neutralization reactions) may take place in solutions of selenium oxychloride. The conductance titration method has proved to be useful in the study of these reactions.

A part of the experimental work upon which this paper is based was supported by a special direct grant from the Polytechnic Institute of Brooklyn. The author takes this opportunity gratefully to acknowledge this grant as well as the assistance of Mr. Louis Lento, Mr. Alvin Gordon, and Mr. Julius Jackson, who have acted as Research Assistants in Selenium Oxychloride Investigations. The author is pleased to acknowledge his indebtedness to his colleagues, particularly to Professors B. P. Caldwell and R. E. Kirk, whom he has frequently consulted.

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REDUCTION OF PERRHENATE[1,2]

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Received February 14, 1938

Perrhenates when heated with hydrogen may be reduced to elementary rhenium and if heated with sulfur dioxide to colored compounds of intermediate valence. In solution the result obtained depends not only on the particular reducing agent but also on other factors such as concentration and temperature.

REDUCTION WITH HYDRIODIC ACID

In 1931 Krauss and Steinfeld (15) heated a mixture of potassium perrhenate, potassium iodide, and concentrated hydrochloric acid on a sand bath and crystallized potassium chlororhenate, K_2ReCl_6, from the reaction mixture. They thought that they had evidence that a salt of trivalent rhenium was also produced but Enk (4), who followed the same general procedure, found only the chlororhenate. I and W. Noddack (19) studied the reaction quantitatively by measuring the amount of iodine set free. They found that it represented a decrease in the valence of the rhenium from 7 to 4. Jakób and Jezowska (14) have described a compound of pentavalent rhenium, K_2ReOCl_5, which they obtained by reducing potassium perrhenate with 2 equivalents of hydriodic acid in the presence of hydrochloric acid. In dilute acid this salt, according to these authors (14), undergoes disproportionation to compounds of valence 7 and valence 4:

$$3Re^{+5} = 2Re^{+4} + Re^{+7}$$

Such a disproportionation was noted by Geilmann and Wrigge (7) in the case of rhenium pentachloride.

Jakób and Jezowska (14) found rhenium of valence 4 to be formed when they used 3 equivalents of hydrogen iodide. Young and Irvine (24) carried out the reaction between potassium perrhenate and hydrogen iodide

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[1] This paper was presented at the Second Annual Symposium of the Division of Physical and Inorganic Chemistry of the American Chemical Society, held at Cleveland, Ohio, December 27-29, 1937.

[2] Contribution No. 67 from the Research Laboratory of Inorganic Chemistry of the Massachusetts Institute of Technology.

in a closed system in an atmosphere of carbon dioxide. They converted iodides to chlorides by successive additions of hydrochloric acid and by subsequent removals of volatile compounds at low temperatures and low pressures. The valence of the rhenium in the final residue was found to be 4.

REDUCTION WITH SOLUTIONS OF CERTAIN OXIDIZABLE SALTS

Hölemann (12) wished to relate the color of a reduced perrhenate solution to the valence of the rhenium. This he was unable to do because the color depends not only on the valence of the rhenium but also on the components of the solution. He studied the reduction potentiometrically and found that ferrous sulfate, stannous sulfate, and titanous sulfate in rather concentrated sulfuric acid solutions caused reduction to valence 5, as did stannous chloride in 15 per cent hydrochloric acid. Chromous sulfate, however, reduced the perrhenate in sulfuric acid to a compound of tetravalent rhenium. This fact was also noted by Turkiewicz (21).

Briscoe, Robinson, and Stoddart (2) obtained a black compound by the action on perrhenate of both hydrazine hydrate and stannous chloride. This they assumed to be the dihydrate of rhenium dioxide. I and W. Noddack (19) also obtained a compound of tetravalent rhenium, K_2ReCl_6, by the latter reagent. The results of Hölemann, of Briscoe, Robinson, and Stoddart, and of I. and W. Noddack seem compatible when it is recalled that compounds of pentavalent rhenium undergo disproportionation readily and that those containing the element in the tetravalent state are easily hydrolyzed. When Hölemann (11) carried out the reduction in hydrochloric acid solution with stannous chloride in the presence of potassium thiocyanate, he found that the rhenium was reduced to valence 4. Druce (3), however, was able to isolate rhenium oxythiocyanate, $ReO(CNS)_4$, from the products of such a reaction.

REDUCTION WITH METALS

The varied results obtained with zinc as the reducing agent may be due in part, at least, to the difference in concentration of the acid. Briscoe, Robinson, and Stoddart (2), using zinc and dilute hydrochloric acid, obtained the dihydrate of rhenium dioxide. They thought this to be the sole product and that the compound could be used in the quantitative determination of rhenium. The material obtained by Geilmann and Hurd (6) by a similar process contained a mixture of the dioxide, lower oxides, and rhenium metal. Young and Irvine (23) found in studying reductions of perrhenic acid with cadmium that, provided the concentration of hydrochloric acid remained above 7 *N*, chlororhenates were produced almost exclusively, and at concentrations between approximately 7 *N* and 3 *N* for the most part chlororhenates and the hydrated dioxide, but at lower concentrations considerable lower oxide was also formed. This latter increased in amount with decreasing acid concentration, and if the hydrochloric acid was less than 0.2 *N* the product consisted of approximately 75 per cent $ReO_2 \cdot 2H_2O$ and 25 per cent $ReO \cdot H_2O$.

Advantage was taken of the solubility of the dioxide in concentrated hydrochloric acid to separate it from the lower oxide. Since the valence of the rhenium in the solution was found to be 4, the absence of Re_2O_3 was proved, as it is also soluble in concentrated hydrochloric acid. The residue was analyzed for rhenium; the valence of the element was obtained by ignition of the compound in oxygen in a closed system over mercury; the amount of water associated with the compound was obtained by reduction with hydrogen. By a similar procedure a lower oxide, $Re_2O \cdot 2H_2O$ was obtained by reduction with zinc. Both lower oxides are black and not readily attacked by dilute alkaline chromate or acid ferric sulfate, but are rapidly attacked by nitric acid and bromine water.

Lundell and Knowles (16) have reported the formation of a rhenide, in which the rhenium possesses a valence of -1, by the passage of a dilute sulfuric acid solution containing perrhenic acid through a Jones reductor.

REDUCTION BY ELECTROLYSIS

Rhenium may be plated out directly on various metals from dilute sulfuric acid solutions of perrhenic acid as has been reported by Fink and Deren (5) and by Lundell and Knowles (16). Compounds of intermediate valence, however, may be obtained if the acid used is at least moderately strong. Jakób and Jezowska (13) were able to obtain rhenium of valence 5 by carrying out the electrolysis in hydrochloric acid of concentration greater than 7 *N*, and lower oxides in a concentrated sulfuric acid solution. With 1 *N* acid they isolated lower oxides. Schmid (20) likewise produced compounds containing rhenium of intermediate valences, 4 and 3, in solutions of 6 *N* hydrochloric acid. Cathodes of both palladium and platinum were used in these investigations.

Hölemann (10, 9) employed an electrolyte of ammonium bifluoride in the hope of obtaining an insoluble fluoride of trivalent rhenium, but the metal was formed directly. With a platinum cathode he obtained both metal and oxide from dilute hydrochloric acid solutions and also from 4 *N* sulfuric acid. By the use of a mercury cathode, however, rhenium amalgam and the dioxide were produced.

REDUCTION OF POTASSIUM CHLORORHENATE

In confirmation of the work of Schmid (20), who obtained an olive-green solution containing Re^{+3} by the electrolytic reduction of perrhenic acid in

6 *N* hydrochloric acid, are the results obtained by Hölemann (10) and by Manchot and coworkers (17, 18) in the reduction of potassium chlororhenate, K_2ReCl_6. Hölemann (10) used a mercury cathode and a solution of hydrochloric acid and obtained rhenium amalgam and an olive-green solution. A green solution was also noted by Manchot and coworkers (18), who employed 1 molar sulfuric acid and both mercury and platinum cathodes. The rhenium in the solution was found by them to be trivalent. The same result was obtained with zinc as the reducing agent, the other factors remaining the same. A compound of trivalent rhenium was not, however, isolated.

Rhenium trichloride produced by the chlorination of rhenium gives a deep red water solution entirely different from the solution described by Manchot and coworkers as containing trivalent rhenium. This may be due to the fact that the anhydrous compound is a dimer, as has been recently found by Wrigge and Biltz (22) from molecular weight determinations in glacial acetic acid. The suggestion of Manchot and Düsing (17) that the rhenium trichloride, produced by Geilmann, Wrigge, and Biltz (8), may have been partially oxidized has been refuted by the latter (1).

SUMMARY

In conclusion, it may be said that the results, in general, described by the various investigators of the reduction of perrhenate show that by the use of the most active reducing agents rhenium metal may be formed, but that compounds containing rhenium of intermediate valences may also be produced, especially at rather high acid concentrations. Such compounds may also be formed by the less active reducing agents. The behavior of perrhenate on reduction coincides with what might be predicted of an element between tungsten and osmium in the periodic classification.

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ALIPHATIC DIAZO COMPOUNDS, NITRONES, AND STRUCTURALLY ANALOGOUS COMPOUNDS

SYSTEMS CAPABLE OF UNDERGOING 1, 3-ADDITIONS

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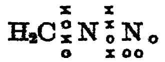
Received April 28, 1937

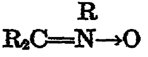
There are a number of substances, containing systems of double bonds and semipolar bonds, which are capable of undergoing 1, 3-addition. These are all extremely interesting compounds chemically, especially from the standpoint of electronic linkages, for in all of them the middle element in the 1, 3-system is a "pentavalent" nitrogen atom. This atom is joined on one side by a double bond to carbon or nitrogen, and on the other side to oxygen, nitrogen, or carbon by a semipolar double bond alone, or by a semipolar bond *and* a covalent bond. In all the 1, 3-additions the "pentavalent" nitrogen in the middle apparently takes no part except that its valence drops from "5" to 3. The most important of these systems are:[1]

1. The aliphatic diazo compounds, typified by diazomethane, CH_2N_2 (page 194).

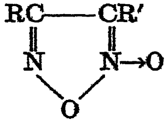


$CH_2{=}N{\rightleftarrows}N$ or $H_2C\begin{smallmatrix}x\\o\\x\\o\end{smallmatrix}N\begin{smallmatrix}x\\x\\o\\x\end{smallmatrix}\underset{oo}{N}{}_o$

2. The azides, $RN{=}N{\rightleftarrows}N$ (page 214).



3. The *N*-ethers of the oximes, $R_2C{=}\overset{R}{N}{\rightarrow}O$ (nitrones) (page 222).
4. The nitrile oxides, $RC{\equiv}N{\rightarrow}O$ (page 233).
5. The furoxans of Wieland and Semper (382)



and related substances (page 237).

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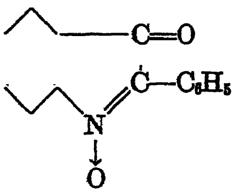
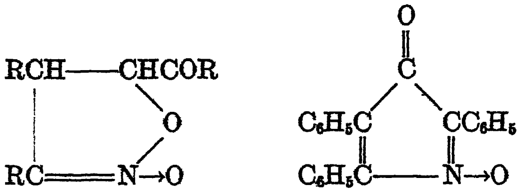
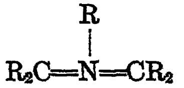
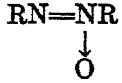
[1] The use of two different symbols for the (outer) electrons of the elements involved in the formation of the compounds discussed in this paper does not in any way imply that the electrons are of different sorts or that the electrons originally belonging to one atom can be identified once the bond between two atoms is formed. The symbols are employed simply because their use renders it somewhat easier to follow the mechanism whereby the bond was formed. The arrow in the formulas designates a semipolar bond formed by a pair of electrons donated by a single atom, and the arrow points from the donor atom to the acceptor atom.

6. The isatogens of Pfeiffer (284) and Ruggli (308) (page 244).

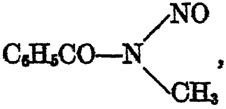
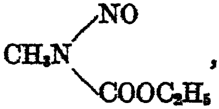


7. The isoxazoline oxides and the cyclic nitrones of Kohler (page 255).

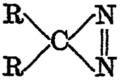


8. Staudinger's nitrenes (340)  $R_2C{=}\overset{\overset{\displaystyle R}{|}}{N}{=}CR_2$ (page 267).
9. The azoxy compounds  $RN{=}\underset{\underset{\displaystyle O}{\downarrow}}{N}R$ (page 272).

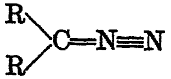
I. THE ALIPHATIC DIAZO COMPOUNDS

The first aliphatic diazo compound was discovered in 1883 by Curtius (85), who obtained ethyl diazoacetate, $CHN_2COOC_2H_5$, as a yellow oil by the action of nitrous acid upon glycine ester hydrochloride. Diazomethane, CH_2N_2, was prepared by v. Pechmann (271) in 1894 by treating *N*-methyl-*N*-nitrosobenzamide,  $C_6H_5CO{-}N\begin{smallmatrix}\diagup NO\\ \diagdown CH_3\end{smallmatrix}$, methylnitrosourethan,  $CH_3N\begin{smallmatrix}\diagup NO\\ \diagdown COOC_2H_5\end{smallmatrix}$, and other nitroso derivatives of methylamine with alkali. Since then many other aliphatic diazo compounds have been prepared, and by a variety of methods.

Only recently has it become possible to reach a definite conclusion regarding the structures of the aliphatic diazo compounds and the closely related azido compounds. Since the arguments concerning the structure of these compounds have been reviewed recently (332), only a brief outline of this topic will be given here. Curtius (86) originally used the ring formula,

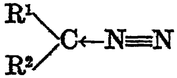


which was accepted for many years until Angeli (7, 8) suggested the open-chain formula


$$R_2C{=}N{\equiv}N$$

Thiele (355), as a result of the work of Staudinger (337), also advocated the open-chain formula. Further work, either of a physical or chemical nature, led to ambiguous results. On the physical side the evidence was interpreted by some workers in favor of the ring structure (149, 214, 216), by others in favor of the chain formula (26), while a third group believed that the physical evidence, especially that based upon the parachors, was inconclusive (248, 127, 331). On the chemical side the evidence was no less conflicting, for the methods of preparation (337, 343) as well as the reactions of these compounds (92, 117, 339, 341) could be interpreted on the basis of either formula.

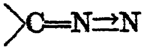
It became obvious, of course, that the Angeli formula, containing a pentacovalent nitrogen atom, could not be correct, and Langmuir (202, 203) proposed the structure $R_2C{=}N\overset{\rightarrow}{=}N$, which is isosteric with the ketenes (20, 226, 227). Another electronic modification of Angeli's formula


$$R^1R^2C{\leftarrow}N{\equiv}N$$

in which the middle nitrogen atom donates two electrons to the carbon atom, has been considered. Compounds possessing such a structure should be resolvable, by analogy with the sulfones which were resolved by Phillips (286, 287, 288). Attempts were made to prepare optically active aliphatic diazo compounds (81, 207–212, 224, 259, 260, 261, 335), and while the products in some cases showed a slight optical activity, it remained for Ray (302, 303) to suggest, and for Weissberger (358, 359) to prove, that the optical activity was due to impurities present in the diazo compounds.

The results of Boersch (55) on the electron diffraction of the molecule of diazomethane have shown conclusively that the chain formula is the correct one, but the low dipole moment of the aliphatic diazo group (333) excludes either of the two chain formulas alone. However, the only difference between the two chain formulas lies in the distribution of the electrons and, if the aliphatic diazo compounds are regarded structurally not merely as one of the two possible chain structures but as a resonancehybrid of both, then the low value for the dipole moment and the lack of optical activity are not anomalous.

The conclusion, therefore, as to the structure of these substances is that the open-chain formula is correct, and that the compounds are resonance-hybrids of the two electronic structures



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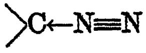
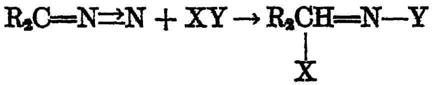


and, as Sidgwick says (reference 332, page 362), "it is one of the few groups of organic chemistry for which no one formula can be written, even as an approximation."

Either of these two structures might be expected to undergo 1,3-additions, one group becoming attached to the end nitrogen atom and the other to the carbon atom. There are a great many chemical reactions of this type and these reactions constitute, in themselves, independent evidence that the open-chain form actually exists. In these reactions the middle nitrogen atom always drops in valence from "5" to 3, while the ends of the system become attached to the two adding groups, thus:



$$R_2C{=}N\stackrel{\rightarrow}{=}N + XY \rightarrow R_2\underset{\displaystyle X}{\underset{|}{C}}H{=}N{-}Y$$

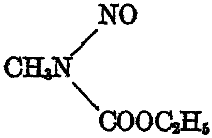
A. Preparation of aliphatic diazo compounds

(*1*) By the action of nitrous acid on aliphatic amino acids. This method is decidedly limited, but when it can be used it is usually the best method. The amine must be primary and the amino group must be joined to a carbon atom holding at least one hydrogen atom which is also alpha to a complex containing a multiple bond but no free hydroxyl group. Thus compounds containing the groups $H_2N\underset{|}{C}HCOOC_2H_5$, $H_2N\underset{|}{C}HC{\equiv}N$, and $H_2N\underset{|}{C}HCOR$ all give aliphatic diazo compounds when their hydrochlorides are treated with nitrous acid, while compounds containing groups such as $H_2N\underset{|}{C}HCOOH$, $H_2NCH(CH_3)_2$, and $H_2NC(CH_3)_2COOC_2H_5$ do not. The latter compounds give only alcohols, the usual reaction of primary aliphatic amines with nitrous acid.

(*2*) For the diazo hydrocarbons other methods must be used. Diazomethane and diazoethane are usually prepared by the method of v. Pechmann (271, 272, 276, 366, 222) from methylnitrosourethan. Methylnitrosourethan and ethylnitrosourethan are now commercial products. They are prepared as follows:

$$2CH_3NH_2 + ClCOOC_2H_5 \rightarrow CH_3NHCOOC_2H_5 + CH_3NH_2\cdot HCl \xrightarrow[NaOH]{ClCOOC_2H_5} CH_3NHCOOC_2H_5$$

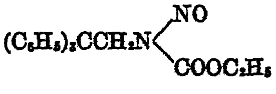
$CH_3NHCOOC_2H_5$ + oxides of nitrogen (from $As_2O_3 + HNO_3$) in ether →



$$CH_3N\begin{cases}NO\\COOC_2H_5\end{cases}$$

Methylnitrosourethan is a yellowish-red liquid which boils at 70°C. at 27 mm. It is very toxic and irritating to the skin, lungs, and eyes. The best method of converting methylnitrosourethan to diazomethane is as follows: 5 g. of sodium is dissolved in the minimum amount of methanol, about 50 to 75 ml., by heating. This solution is placed in a small distilling flask equipped with a small dropping funnel and connected to a condenser through which ice water circulates (if the tap water is at all warm it must be cooled). The methylnitrosourethan is dissolved in some absolute ether and put in the dropping funnel. The substance to be methylated is dissolved in absolute ether, cooled in an ice-salt bath, and set under the delivery end of the condenser. When all is ready the methylnitrosourethan is run slowly into the sodium methoxide, the ether and diazomethane distilling over. There must always be ether in the reaction flask to distill over with and to dilute the diazomethane. After all of the methylnitrosourethan has been added, absolute ether is added with continuous slow distillation until the distillate is no longer yellow. From 10 ml. of methylnitrosourethan dissolved in 50 ml. of ether one obtains an ethereal solution containing 1.8 to 2.0 g. of diazomethane. This represents a yield of about 50 to 80 per cent. Diazomethane does not keep well, so it should be made up from methylnitrosourethan just before it is to be used. For diazoethane the same procedure is used, substituting ethylnitrosourethan for the methylnitrosourethan and (most important) ethyl alcohol for the methyl alcohol. As an example of the preparation of a more complicated diazo compound by this method, the preparation of triphenylmethyldiazomethane may be cited (153):

$(C_6H_5)_3CCH_2NH_2 \rightarrow (C_6H_5)_3CCH_2NHCOOC_2H_5 \rightarrow$

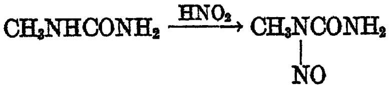


$$(C_6H_5)_3CCH_2N\begin{cases}NO\\COOC_2H_5\end{cases} \rightarrow (C_6H_5)_3CCHN_2$$

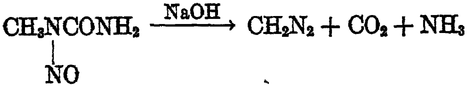
(orange-yellow; m.p. 78–80°C. (decomposition))

The method of Arndt (18, 17, 269, 361), using methylnitrosourea, permits the use of a much higher concentration of diazomethane, for 6 g. of it may be obtained from 20 g. of the urea. Moreover methylnitrosourea is a solid and it does not have the irritating action of methylnitrosourethan, although it does not keep well and on standing in a warm place for a long time may undergo spontaneous decomposition which may become rather violent. Hence it must be kept cold and dry. It is best not to prepare more than 25 to 50 g. of it at any one time. The reactions involved are as follows:

$$KOCN + CH_3NH_2\cdot HCl \longrightarrow CH_3NHCONH_2 + KCl$$

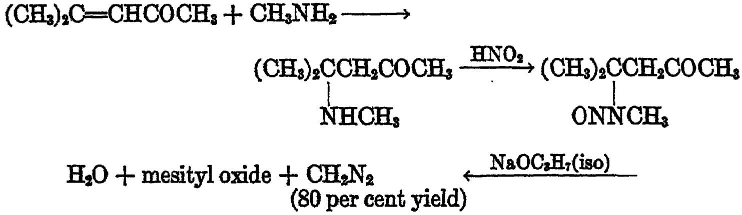


$$CH_3NHCONH_2 \xrightarrow{HNO_2} CH_3\underset{\underset{NO}{|}}{N}CONH_2$$



$$CH_3\underset{\underset{NO}{|}}{N}CONH_2 \xrightarrow{NaOH} CH_2N_2 + CO_2 + NH_3$$

In the method of Jones and Kenner (168–170; see also references 160 and 343) nitroso-β-alkylaminoketones are employed, especially those derived from mesityl oxide.



$$(CH_3)_2C{=}CHCOCH_3 + CH_3NH_2 \longrightarrow (CH_3)_2\underset{\underset{NHCH_3}{|}}{C}CH_2COCH_3 \xrightarrow{HNO_2} (CH_3)_2\underset{\underset{ONNCH_3}{|}}{C}CH_2COCH_3$$

$$H_2O + \text{mesityl oxide} + \underset{(80\text{ per cent yield})}{CH_2N_2} \xleftarrow{NaOC_3H_7(iso)}$$

(*3*) The method of Staudinger and Kupfer (344), using hydrazine, chloroform, and alkali, gives a yield of about 25 per cent.

$$H_2NNH_2 + CHCl_3 + KOH \rightarrow CH_2N_2 + 3KCl + 3H_2O$$

A similar method is that of Bamberger and Renauld (35), using *N*,*N*-dichloromethylamine and hydroxylamine

$$CH_3NCl_2 + H_2NOH \rightarrow 2HCl + H_2O + CH_2N_2$$

but this method is of little value because of the difficulties involved in handling the chloroamines.

(*4*) The method of Staudinger, involving the oxidation of the hydrazones of ketones, is always the best method to be used for the complicated diazo hydrocarbons (338, 108, 258). Thus benzophenone hydrazone reacts with mercuric oxide in petroleum ether at room temperature, and in 5 to 6 hr. diphenyldiazomethane is obtained in 85 to 98 per cent yields. This is a deep red solid which melts at 29–30°C., and which can be recrystallized from methanol, although there is some decomposition to give the ketazine, $(C_6H_5)_2C{=}N{-}N{=}C(C_6H_5)_2$.

$$(C_6H_5)_2C{=}N{-}NH_2 \xrightarrow{HgO} (C_6H_5)_2C{=}N\rightleftarrows N$$

Phenylbenzoyldiazomethane may be prepared in a similar manner:

$$\begin{array}{l} C_6H_5C{=}N{-}NH_2 \\ \quad | \\ C_6H_5CO \end{array} \longrightarrow \begin{array}{l} C_6H_5C{=}N\rightleftarrows N \\ \quad | \\ C_6H_5CO \end{array}$$

For the assay of diazomethane solutions there are three methods: (*a*) The method of Marshall and Acree (223) is considered the best. The diazomethane solution (20 ml.) is cooled and treated with an excess of ethereal $N/10$ benzoic acid solution. After the reaction

$$C_6H_5COOH + CH_2N_2 \rightarrow C_6H_5COOCH_3 + N_2$$

has taken place the excess of benzoic acid is determined by titrating with $N/10$ barium hydroxide, using phenolphthalein as the indicator. The solution must be diluted with much water before titrating and should be shaken vigorously during the titration. (*b*) The diazomethane solution may be directly titrated with standard alcoholic hydrochloric acid (235):

$$CH_2N_2 + HCl \rightarrow CH_3Cl + N_2$$

(*c*) The method of v. Pechmann (271). An excess of standard iodine is added and the excess then titrated in the usual way.

$$CH_2N_2 + I_2 \rightarrow CH_2I_2 + N_2$$

(*d*) Either of the reactions in (*a*), (*b*), or (*c*), but preferably that in (*b*), may be used, and the evolved nitrogen collected and measured.

B. Properties of the aliphatic diazo compounds

The volatile diazo hydrocarbons are yellow gases or liquids; when solid they are usually reddish. Diazomethane is easily condensed to a liquid boiling at −23° to −24°C. and, since the vapor of it is explosive, no more than a gram or so should ever be handled at once. In ethereal or other solution, however, it is quite safe, but even the ethereal solution will explode if heated to about 200°C. Diazomethane is said to be violently poisonous, attacking the eyes and lungs, although some people are said to be unaffected by it. One should observe due, though not necessarily extreme, precautions in handling either it or the methylnitrosourethan from which it is made (219, 18, 255).

The diazocarbonyl compounds, particularly the diazo esters, are yellow liquids with characteristic odors. The color deepens when they are heated and returns to the lighter shade on cooling. They are quite volatile, and the volatility decreases with the molecular weight of the ester group, while the solubility in water falls off. They can be distilled with steam or *in vacuo*. They are quite soluble in most organic solvents and sparingly soluble in water. The esters can be hydrolyzed to salts with dilute aqueous alkali, but the free acids decompose as fast as they are formed, and even carbon dioxide acts upon the salts in the cold, leading to decomposition products.

C. Reactions of diazomethane

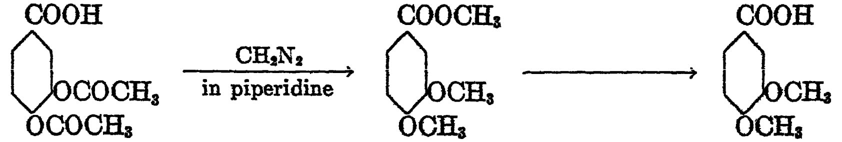
Probably the most important use of diazomethane is as a methylating agent. For this purpose it is usually used in solution in ether, although alcohol (158), chloroform (137), methylal (111), or any other inert solvent may be used. The preparation of an ethereal solution of the reagent is not always necessary, for the methylation may be carried out by mixing the compound to be methylated with methylnitrosourethan or methylnitrosourea in alcoholic solution and then adding a mildly alkaline compound which is insoluble in the alcohol (to avoid an excess), such as potassium carbonate (225).

The reagent is especially suited for the methylation of phenols and carboxylic acids, and the velocity of the methylation increases with the acidity of the compound. The reaction is usually fast and quantitative, the excess of the reagent being easily removed by adding a little hydrochloric acid; there are no by-products other than nitrogen and perhaps a small amount of the polymer of the reagent. If the methylation is slow, more diazomethane is added until the yellow color is permanent after standing overnight.

Diazomethane is a very valuable, mild methylating agent, excellent for use with sensitive compounds, as it reacts in neutral solution. Only the cost, the danger in handling, and the toxicity of the nitrosourethan and of diazomethane itself have kept it from becoming the ideal methylating agent.

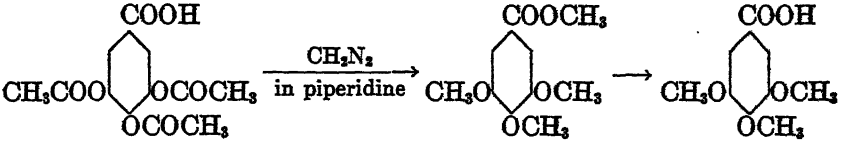
Ortho substituents in benzene derivatives hinder the methylation or may block it completely (157). Thus salicylic ester does not methylate, while gallic acid gives the trimethoxy methyl ester and pyrogallolcarboxylic acid gives the 3,4-dimethoxy-2-hydroxy methyl ester. However, picric acid gives trinitroanisole, and v. Pechmann (277) was able to obtain the esters of mesitylenecarboxylic acid, symmetrical-tribromobenzoic acid, mellitic acid, and trinitrobenzoic acid. The reagent is unsuitable for preparing ester acids of the dibasic acids, as the main products are the diesters and unchanged acids (357).

Phenol esters are usually converted to the ethers, the —OCOR group being replaced by —OCH_3, but —$NHCOCH_3$ is not affected. This gives a method of determining whether an acetylaminophenol is an *O*-acetyl or an *N*-acetyl derivative. Nierenstein (254) has developed a new method of methylating the phenol esters in this way by the action of diazomethane in the presence of piperidine. Each molecule of piperidine removes one acetyl group, which is then replaced by methyl. This has the advantage that the acetyl derivatives are well-crystallized, sharply melting compounds which are easily obtained in the pure state.



Diacetylprotocatechuic acid

Veratric acid



Triacetylgallic acid

Trimethyl ether of gallic acid

Alcohols are not usually methylated by diazomethane, but in the presence of alkoxides of the polyvalent metals they do react (228).

$n\text{-}C_4H_9OH + 5$ per cent $Al(OC_2H_5)_3 + CH_2N_2 \rightarrow 83$ per cent yield of $n\text{-}C_4H_9OCH_3$

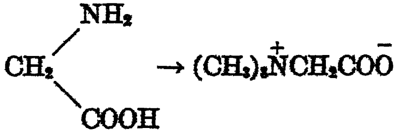
iso-C_3H_7OH similarly → 77 per cent yield of iso-$C_3H_7OCH_3$

$n\text{-}C_4H_9OH + Sb(OC_4H_9)_3 + CH_2N_2 \rightarrow 73$ per cent yield of $n\text{-}C_4H_9OCH_3$

Enols are usually methylated.

Acids are rapidly transformed to methyl esters, and the method is equal in effectiveness to the method using the silver salt and methyl iodide.

Nierenstein (136) states that diazomethane does not methylate amino acids, but Biltz and Paetzold (50) have shown that glycine, in the presence of a trace of water, is quantitatively converted into betaine:



$$CH_2\begin{cases} NH_2 \\ COOH \end{cases} \rightarrow (CH_3)_3\overset{+}{N}CH_2CO\overset{-}{O}$$

and that other amino acids of molecular weight greater than that of alanine react normally with methylation of both the amino and the carboxyl groups (156).

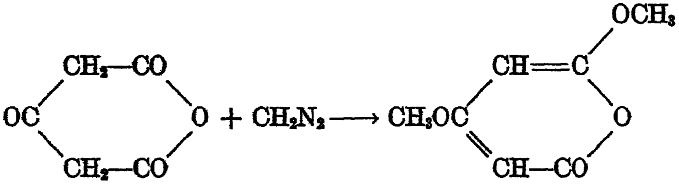
Oximes give the *O*-methyl ethers, although the *syn*- and *anti*-forms of the oximes do not react with equal ease. However, there seems to be no regularity in these differences in reactivity, that is, the *syn*- and *anti*-forms of oximes cannot be distinguished by means of this reaction. There is no explanation for these differences, though it probably has to do with differences in the dissociation constants of the two oximes. The *anti*-form of benzaldoxime gives an *O*-methyl ether, while the *syn*-form does not react (123). Not much systematic work has been done on the methylation of oximes with diazomethane.

Primary *amines* are converted into secondary methylamines, though the reaction has not been much used:

$$RNH_2 + CH_2N_2 \rightarrow RNHCH_3 + N_2$$

Secondary amines do not react, and acetylation protects primary amines completely against the action of the reagent (272).

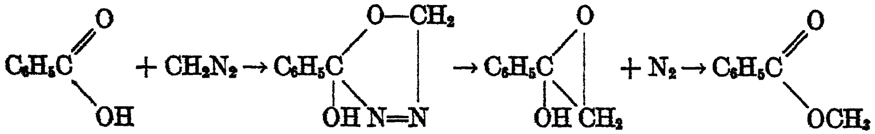
Benzoic anhydride gives methyl benzoate and a diazoketone; succinic anhydride gives methyl succinate (57); acetonedicarboxylic anhydride gives an 80 per cent yield of 4,6-dimethoxy-α-pyrone (218).



Phthalimide and succinimide give the *N*-methyl derivatives smoothly (201).

Acetoacetic ester reacts slowly, giving β-methoxyethyl crotonate, but malonic ester does not react at all under ordinary conditions (273).

In the methylations considered so far the mechanism of the reaction is obscure and no intermediates have been isolated. It is possible to write them as 1,3-additions, thus:



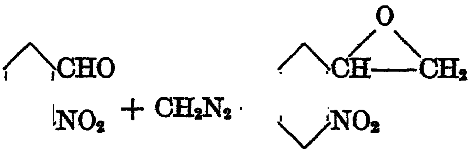
This is in analogy with the known addition of aliphatic diazo compounds to C—C multiple bonds to give five-membered rings, but in the absence of definite proof this mechanism can only be accepted provisionally.

Aldehydes behave toward diazomethane as though they contained an active hydrogen atom, and give methyl ketones (323).

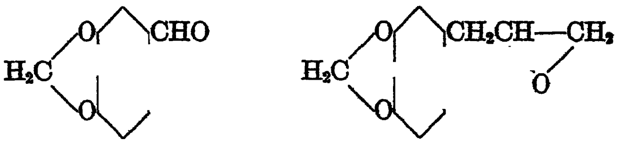
$$C_6H_5CHO + CH_2N_2 \rightarrow C_6H_5COCH_3 + N_2$$

$$n\text{-}C_6H_{13}CHO + CH_2N_2 \rightarrow n\text{-}C_6H_{13}COCH_3 + N_2$$

This reaction bears the name of Schlotterbeck, although Meyer (236) has claimed priority. Arndt and his students (15) have shown that the reaction is not always clean-cut, and so is not of general application, for in some cases ethylene oxides are formed, the ketone appearing only as a by-product. Thus *m*- and *p*-nitrobenzaldehydes give the corresponding acetophenones, but *o*-nitrobenzaldehyde gives *o*-nitrophenylethylene oxide:

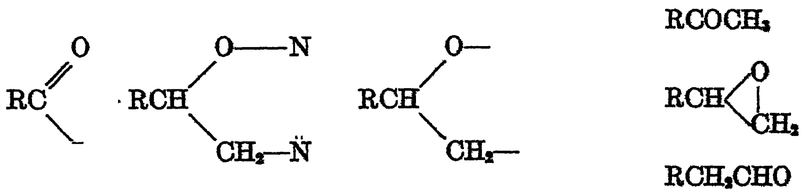


Piperonal reacts with *two* molecules of diazomethane to give safrole oxide (243):



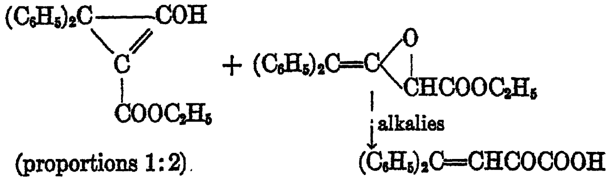
From 10 g. of *p*-nitrobenzaldehyde there was produced 5 g. of the ethylene oxide, 3.2 g. of *p*-nitroacetophenone, and traces of p-$NO_2C_6H_4CH_2COCH_3$ (19).

The mechanism for these reactions suggested by Arndt (see also 226, 227) involves a primary 1,3-addition:

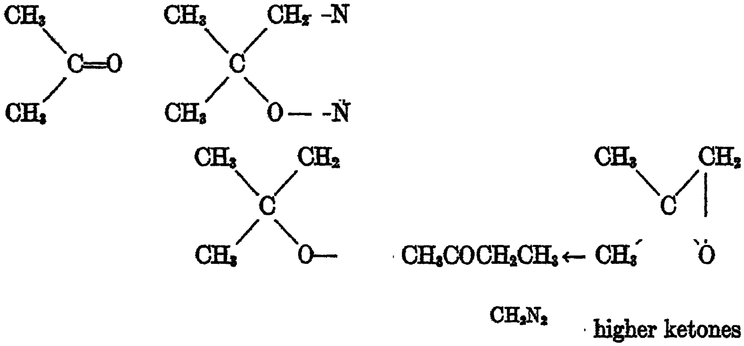


Ketene gives cyclobutanone, possibly *via* cyclopropanone (217) as an intermediate, while diphenylketene reacts with diazoacetic ester as follows (346):

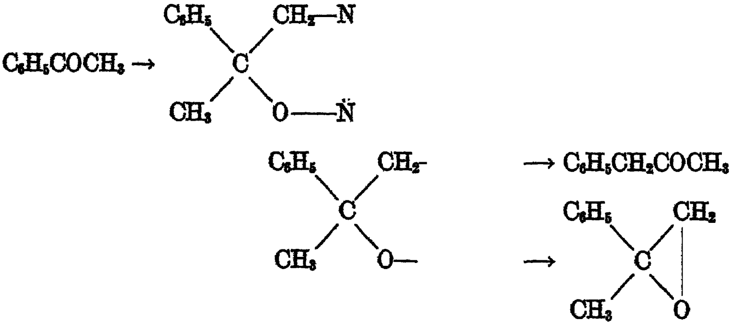
$(C_6H_5)_2C{=}C{=}O + CHN_2COOC_2H_5 \rightarrow$



Ketones do not react under ordinary conditions, but in the presence of catalysts such as water, alcohols, or metallic salts they do react (226, 227). Thus acetone gives α,α-dimethylethylene oxide (40 per cent yield) along with some methyl ethyl ketone and higher ketones:

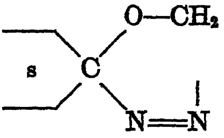


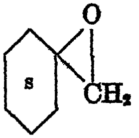
Acetophenone reacts similarly (245):



The cyclic ketones undergo similar reactions, but here the ring enlarges by one carbon atom. Thus cyclohexanone (20 g. in methanol, not in ether, however) reacts vigorously with diazomethane, giving as the main product cycloheptanone (12 g.), with by-products of cyclooöctanone and an oxide isomeric with cycloheptanone. Cyclopentanone similarly gives cycloheptanone as the main product (14 g. from 23 g. of cyclopentanone) with cyclooötanone and the same oxide as by-products (244). This is an excellent method for preparing cycloheptanone.

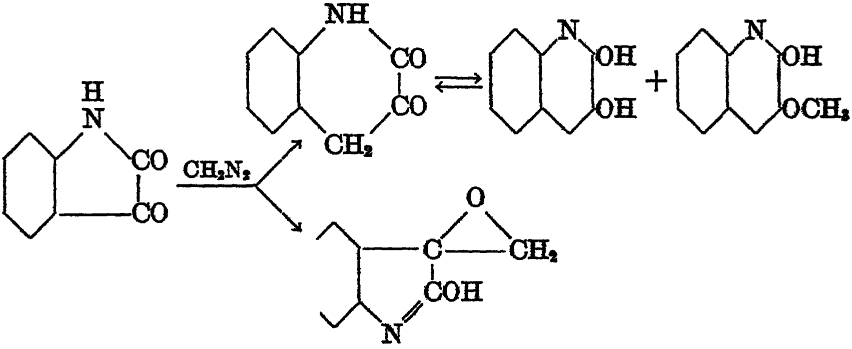
This reaction is also probably a 1,3-addition, giving compound I which then rearranges to II with evolution of nitrogen. II reacts again to give the cycloheptanone. The oxide isomeric with cycloheptanone could well be III.



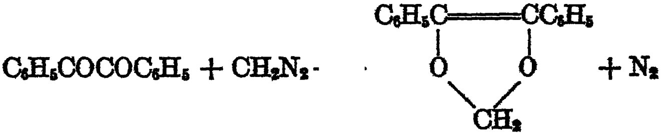


II III

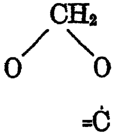
A similar ring expansion occurs when diazomethane reacts with isatin, for the product is dihydroxyquinoline (152, 21):

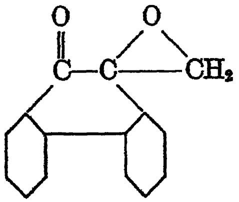


Aliphatic diketones, such as diacetyl and acetonylacetone, are not affected by diazomethane (51), but benzil reacts to give α,β-dihydroxystilbene methylene ether (51, 19); p,p'-dibromobenzil and furil react similarly.

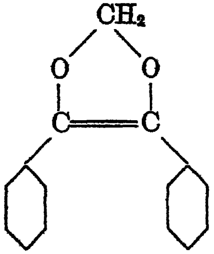


Anthraquinone does not react, but phenanthraquinone with diazomethane plus a trace of methanol gives the ethylene oxide (IV) (19) which, when treated with hydrochloric acid in methanol, gives the chlorohydrin, thus establishing the structure. The acetal (V) is obtained if much methanol is used. Only the acetals VI and VII are produced from benzil and alloxan, and with the latter methylation at both NH groups occurs also.

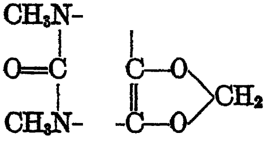




IV



VI



VII

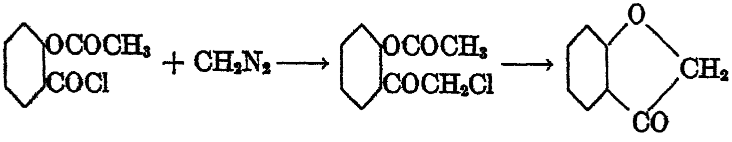
Ortho-quinones such as 6-bromo-1,2-naphthoquinone or 4-triphenylmethyl-1,2-benzoquinone add diphenyldiazomethane in an analogous manner, giving the acetal type of reaction product (106).

The reaction between *acid halides* and diazomethane was originally investigated by Nierenstein and bears his name (84). Nierenstein states that ω-halogenated ketones are formed in good yield:

$$C_6H_5COCl + CH_2N_2 \rightarrow C_6H_5COCH_2Cl + N_2 \quad \text{(72 per cent yield)}$$

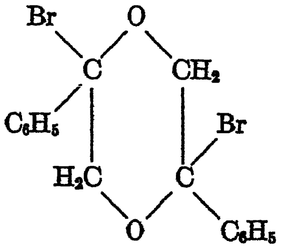
$$C_6H_5CH_2COCl + CH_2N_2 \rightarrow C_6H_5CH_2COCH_2Cl + N_2$$

(84 per cent yield)



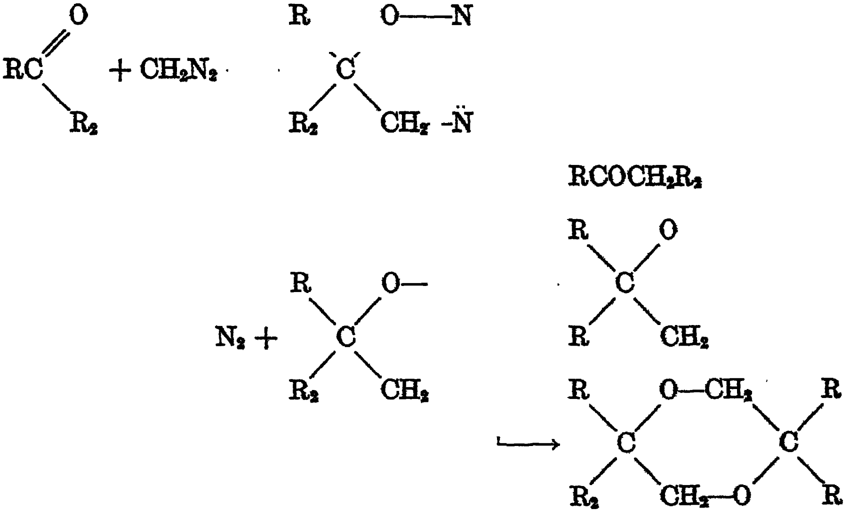
(92 per cent yield)

But the yield of haloketone from benzoyl bromide was small, 62 per cent of the product being the dioxane,



while triphenylacetyl chloride gave the corresponding dioxane in 92 per cent yield (213).

From these results Nierenstein favors the interpretation of the reaction as given by Oliveri-Mandala (264) and by Arndt. In the following R_2 is Cl, Br, or H (so as to include the Schlotterbeck reaction), and the nature of R_2 determines the course of the reaction.



Robinson and his students investigated this reaction (56, 58, 57) and found that benzoyl chloride with diazomethane gave the diazoketone in 91 per cent yield instead of the chloroketone. They were unable to find any trace of substituted dioxanes, although by changing the procedure the ω-chloroketone could be obtained.

$$C_6H_5COCl + 2CH_2N_2 \rightarrow C_6H_5COCHN_2 + CH_3Cl + N_2$$

Thus if the acid halide was added gradually to diazomethane, keeping the latter always in excess, the diazoketone was the main product (reactions A and B), while if the reverse procedure was followed the chloroketone resulted (reaction C).

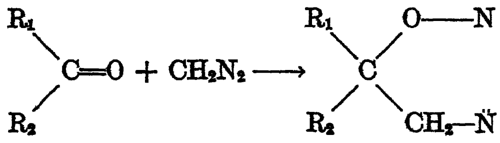
$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 + HCl \tag{A}$$

$$CH_2N_2 + HCl \rightarrow CH_3Cl + N_2 \tag{B}$$

$$RCOCHN_2 + HCl \rightarrow RCOCH_2Cl + N_2 \tag{C}$$

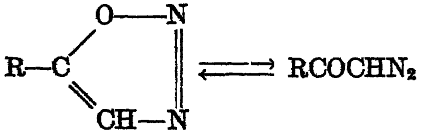
Robinson agrees with Arndt (16) that the diazoketone is the primary product of the reaction. Nierenstein (222) does not agree with this interpretation, however, and continues to write the reaction as above, as merely a special case of the Schlotterbeck reaction.

On the whole it does not seem that Robinson and Nierenstein are as far apart in their interpretations as might be supposed at the first glance. Assuming that the first reaction is a 1,3-addition, we have:



(R_2 is Cl, Br, or H)

If R_2 is halogen, this product can eliminate HX to give:



The action of HX on the diazoketone would give the ω-haloketone, $RCOCH_2X$. If R_2 is not halogen, then the elimination of HX to give the diazoketone cannot occur, but nitrogen can be eliminated to give a radical which could then rearrange to the alkylene oxide or to another ketone, $RCOCH_2R_2$. The elimination of nitrogen in this way might occur even if R_2 were halogen, which would result in an intermediate capable of forming the halogen-substituted dioxanes.

Sulfonyl chlorides are apparently unaffected by diazomethane (23), hence reaction with RCOCl probably involves the carbonyl group, not the chlorine atom.

In three recent papers on aliphatic diazo compounds and electronic structures Arndt and Eistert (20; see also 226, 227) and Eistert (104) have reviewed the Robinson–Ingold–Thorpe electronic conception of organic reactions, applying these to the aliphatic diazo compounds. In the first paper (20) they have shown how the reaction between diazomethane and an acid chloride can be made to give a diazoketone in good yield, and that this in turn can be used as a source for the next higher acid, thus:

$$RCOCl \rightarrow RCOCHN_2 \rightarrow RCH_2COOH$$

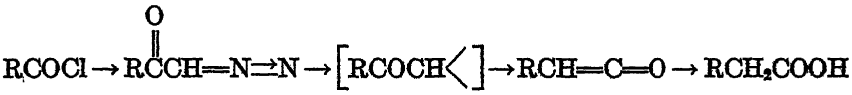
The reactions are

$$RCOCl + 2CH_2N_2 \rightarrow RCOCHN_2 + CH_3Cl + N_2$$

(small amounts of $RCOCH_2Cl$ as by-product). The diazoketone, in the presence of finely divided silver, platinum, or copper (catalyst), reacts with water, alcohols, ammonia, primary amines, or secondary amines (sometimes heating under pressure is necessary) to give nitrogen and derivatives of the next higher acid:

$$\begin{aligned} RCOCHN_2 &+ HOH \rightarrow N_2 + RCH_2COOH \\ &+ R'OH \rightarrow RCH_2COOR' \\ &+ NH_3 \rightarrow RCH_2CONH_2 \end{aligned}$$

The steps in the reaction are much the same as those in the Hofmann-Curtius rearrangement. Instead of an isocyanate a ketene results, which then adds the reagent present to give the final acid or acid derivative:



$$RCOCl \rightarrow R\overset{\overset{O}{\|}}{C}CH{=}N\rightleftharpoons N \rightarrow \left[RCOCH\langle\right] \rightarrow RCH{=}C{=}O \rightarrow RCH_2COOH$$

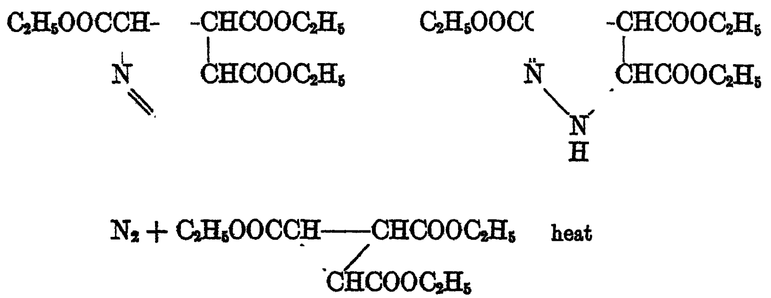
Ammonia and amines, especially aniline, react best of all, while alcohols and water do not react so smoothly. It is best to prepare the amide or anilide and then hydrolyze to the acid. The yields are usually good: thus 18.6 g. of *o*-nitrobenzoyl chloride gave 10 g. of $o\text{-}NO_2C_6H_4CH_2CONH_2$; 19 g. of $\alpha\text{-}C_{10}H_7COCl$ gave 18 g. of $\alpha\text{-}C_{10}H_7COCHN_2$; 10 g. of this gave 6 g. of $\alpha\text{-}C_{10}H_7CH_2COOC_2H_5$, while 5 g. gave 4.2 g. of $\alpha\text{-}C_{10}H_7CH_2CONH_2$; 16 g. of veratroyl chloride gave 15 g. of the diazoketone (this was converted to the amide, from which 4.2 g. of homoveratric acid was obtained); 30 g. of benzoyl chloride gave about 20 g. of phenyl acetamide (328, 304, 385, 342, 329).

The reactions leading to the three products obtainable from an acid chloride and diazomethane, viz., $RCOCH_2Cl$, $RCOCHN_2$, RCH_2COOH, have been developed by Nierenstein (252), Robinson (307), and Arndt (20), respectively. All three may be conducted so as to give excellent yields. To obtain $RCOCH_2Cl$, the acid chloride is kept in excess (diazomethane added dropwise); to get $RCOCHN_2$ the procedure is reversed and the acid chloride dropped into diazomethane; to get RCH_2COOH the second procedure is followed and then H_2O, HOR, NH_3, RNH_2, etc., is added. This latter reaction is catalyzed by finely divided metals.

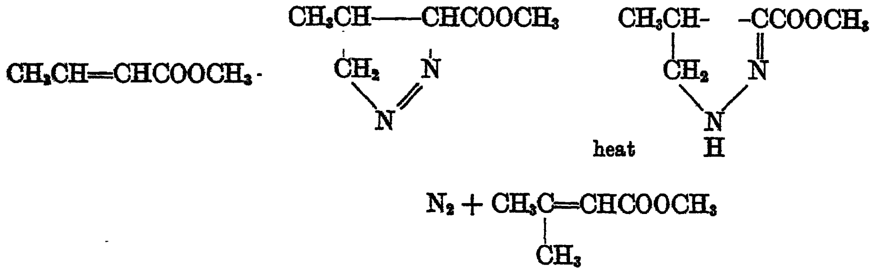
The aliphatic diazo esters in general parallel diazomethane and the other diazo hydrocarbons in their reactions, although no aliphatic diazo compound has been studied to such an extent as diazomethane.

The aliphatic diazo compounds add to carbon–carbon double and triple bonds, especially (though not necessarily) when these are α,β to a carbonyl group or carbethoxyl group. The primary products are pyrazolines formed by direct 1,3-additions. These can frequently be decomposed on heating, especially with polished platinum, to give cyclopropanes. This provides a very good method of preparing some substituted cyclopropanes (280, 74, 1, 164, 31).

$$C_2H_5OOCCH{=}CHCOOC_2H_5 + CHN_2COOC_2H_5 \rightarrow$$



However, the elimination of nitrogen does not always occur completely in the manner shown, for unsaturated open-chain esters often result along with the cyclic ester, or one or the other of these may be the exclusive product (27). Thus:

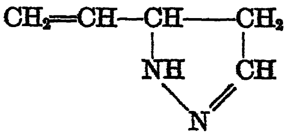


(100 per cent)

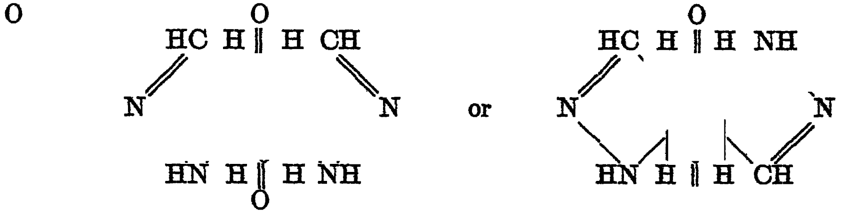
The course of this reaction depends primarily upon the complexity of the pyrazoline,—the simpler members yielding unsaturated esters chiefly, while those compounds containing more ester groups tend to form cyclopropanes.

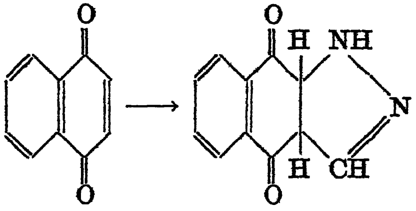
Diazomethane also adds to acetylene to form pyrazole (278) and to ethylene to form pyrazoline (33). Groups such as the cyano or carbethoxyl group favor the addition to ethylenic bonds, while phenyl groups decrease the reactivity (262).

Dienes also react with diazomethane. 5-Vinylpyrazoline was obtained from butadiene when the reaction mixture was kept at −20°C. for 48 hr. (247).

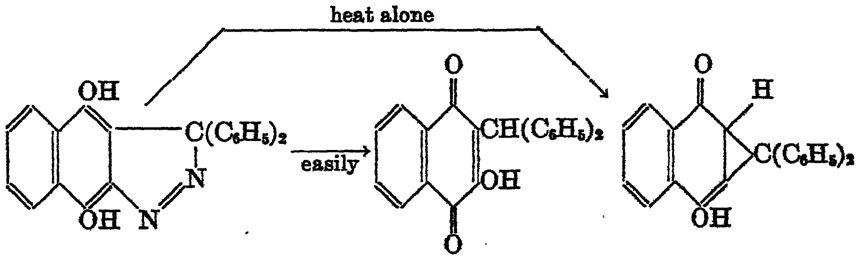


Quinones. v. Pechmann added diazomethane to quinone (279), formulating the reaction in the following way:

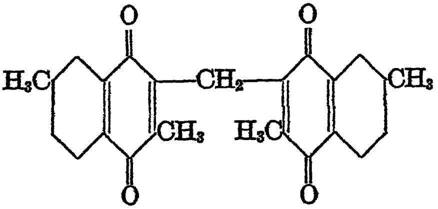




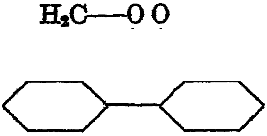
Fieser and Peters (108) added diphenyldiazomethane to α-naphthoquinone and showed that the reaction took the following course:

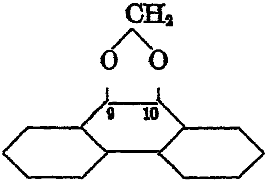


Recently (109) it was found that 2,6-dimethyl-3,4-naphthoquinone did not react with diazomethane, while the corresponding 1,4-naphthoquinone reacted in a peculiar way to give a product derived from two molecules of the quinone:



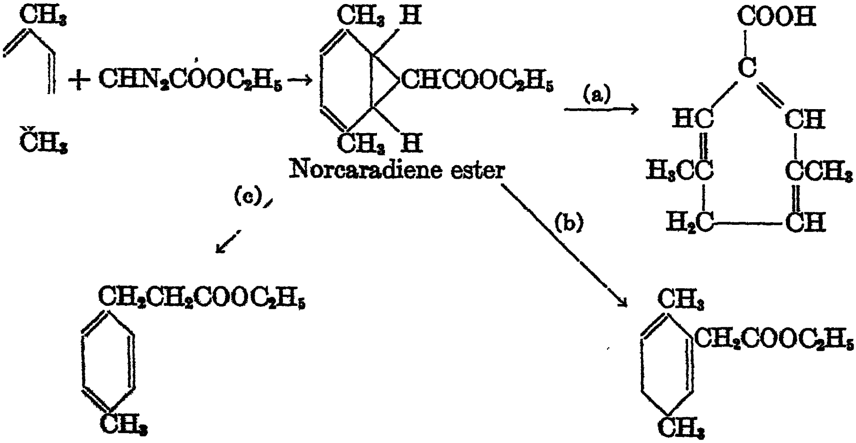
Phenanthraquinone reacts with diazomethane in the presence of a trace of methanol to give spirophenanthroylethylene oxide; in absolute ether or in the presence of 20 per cent of methanol the methylene ether is formed (51, 19):



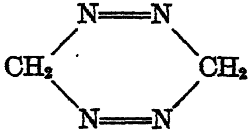


Smith and Pings studied the reaction between diazomethane and duroquinone. The reaction was very complex, but only the carbonyl groups of this substituted *p*-benzoquinone were involved.

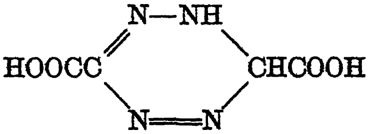
Aliphatic diazo compounds will add to the aromatic double bond, giving as primary products norcaradiene derivatives (71, 75–80, 336). These norcaradiene compounds rearrange easily, giving (*a*) derivatives of cycloheptatriene, (*b*) derivatives of phenylacetic acid, and (*c*) derivatives of *β*-phenylpropionic acid (when the original hydrocarbon contains one or more methyl groups).



Even the polymerization of the aliphatic diazo compounds may be considered as a 1,3-addition. In sunlight diazomethane gives *C*-dihydrotetrazine,



Diazoacetic ester polymerizes in the presence of concentrated alkali to give dihydrotetrazine acids:



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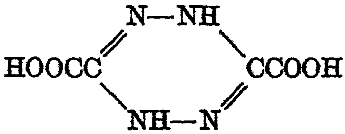
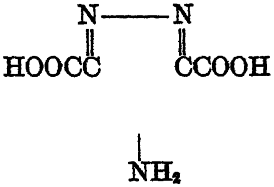
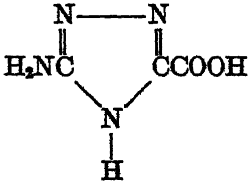
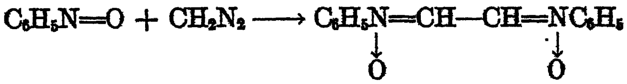


and if the action of the alkali is continued these tetrazine compounds rearrange into amino*triazole* acids such as

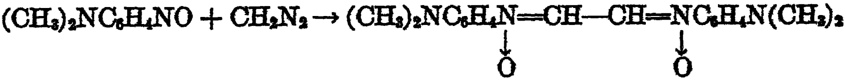




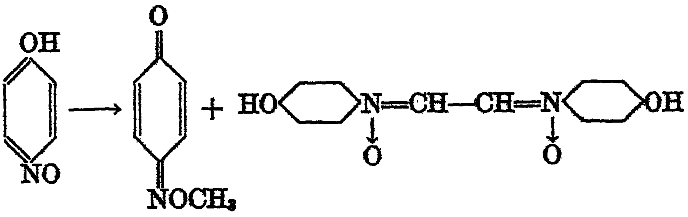
Other *miscellaneous reactions* of diazomethane are as follows: Nitrosobenzene gives diglyoxime *N*-phenyl ether (275) and other nitroso compounds react similarly:



$$C_6H_5N{=}O + CH_2N_2 \longrightarrow C_6H_5\underset{\substack{\downarrow\\ O}}{N}{=}CH{-}CH{=}\underset{\substack{\downarrow\\ O}}{N}C_6H_5$$

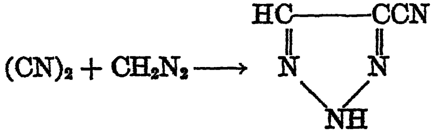


$$(CH_3)_2NC_6H_4NO + CH_2N_2 \rightarrow (CH_3)_2NC_6H_4\underset{\substack{\downarrow\\ O}}{N}{=}CH{-}CH{=}\underset{\substack{\downarrow\\ O}}{N}C_6H_4N(CH_3)_2$$

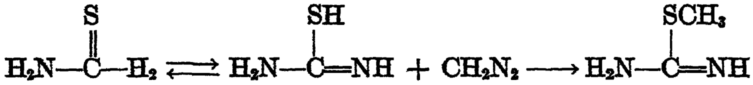


Nitro compounds such as nitromethane, nitrobenzene, etc., are indifferent to diazomethane (151), although v. Pechmann mentions that in the esterification of trinitrobenzoic acid with diazomethane the nitro groups are also attacked (277).

Hydrocyanic acid and cyanogen react rapidly, the former giving acetonitrile and the latter giving a cyanoösotriazole (281):



Urea is unaffected by diazomethane in ether or alcohol, but thiourea is methylated (362).



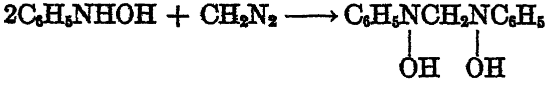
$$H_2N-\overset{\overset{\textstyle S}{\|}}{C}-H_2 \rightleftarrows H_2N-\overset{\overset{\textstyle SH}{|}}{C}=NH + CH_2N_2 \longrightarrow H_2N-\overset{\overset{\textstyle SCH_3}{|}}{C}=NH$$

Hydrogen sulfide reacts with diphenyldiazomethane to give thiobenzohydrol, $(C_6H_5)_2CHSH$, and nitrogen (347).

Hydrazoic acid gives methyl azide and nitrogen with diazomethane (265).

p-Toluenesulfonanilide and *p*-toluenesulfonamide are methylated quantitatively (22).

β-Phenylhydroxylamine gives diphenylmethylenedihydroxylamine (37).

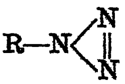


$$2C_6H_5NHOH + CH_2N_2 \longrightarrow C_6H_5\underset{\underset{\textstyle OH}{|}}{N}CH_2\underset{\underset{\textstyle OH}{|}}{N}C_6H_5$$

Other methylations with diazomethane include those in the uric acid series (49, 155), xanthosine (206), uracil (171), and cellulose and the polysaccharides (324, 253).

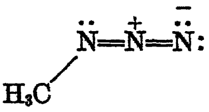
II. AZIDES: RN_3 OR $RN{=}N \rightleftarrows N$ (24)

In the azides the 1,3-system is composed entirely of nitrogen atoms. The compounds may be regarded as analogs of the aliphatic diazo compounds in which the carbon atom at the end of the system, together with the attached groups, has been replaced by a trivalent nitrogen atom with the attached group. As in the case of the aliphatic diazo compounds both cyclic and chain formulas have been used.



and $R-N{=}N \rightleftarrows N$

In 1925 Hendricks and Pauling (154) showed that the azide ion in sodium and potassium azides had a linear configuration and possessed a center of symmetry. Later (73, 163, 178) it was shown that in organic compounds the azido group was linear but did not possess a center of symmetry like the azide ion. The symmetry of the azide ion in aqueous solution is supported by x-ray data and by the data furnished by measurement of the Raman spectra (204). In a recent paper (270) methyl azide was investigated by electron diffraction measurements. The data showed that the azido group was linear, with the methyl group at an angle of about 120° to the line through the azido group, and on the basis of the adjacent charge rule, the two resonance structures favored were



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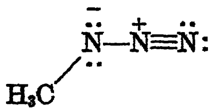


These two formulas are entirely analogous to the two resonance formulas for the aliphatic diazo compounds (332).

The first azido compounds known were the azido derivatives of the aromatic hydrocarbons and the first member of this class, phenyl azide, was obtained by Griess by the action of ammonia upon the diazonium perbromide (146).

$$C_6H_5N_2Br_3 + NH_3 \rightarrow C_6H_5N_3 + 3HBr$$

Since then a number of methods have been developed for the preparation of azides; many of these methods involve the diazonium compounds as reagents, and in most of the methods one reagent contains a chain of two nitrogen atoms, while the third nitrogen atom is supplied by the other reagent—nitrous acid, hydroxylamine, ammonia, etc.—although all three nitrogen atoms may be contained in one reagent.

Thus substituted semicarbazides, such as phenylsemicarbazide, react with sodium hypochlorite to give azido compounds. This reaction is a phase of the Hofmann degradation of an amide, and it has been written in two ways:

$$C_6H_5NHNHCONH_2 \rightarrow C_6H_5N{=}NCONH_2 \rightarrow C_6H_5N{=}NNH_2 \rightarrow C_6H_5N_3 \quad (91)$$

$$C_6H_5NHNHCONH_2 \rightarrow C_6H_5N{=}NCONH_2 \rightarrow C_6H_5N{=}N{-}N{=}C{=}O \rightarrow C_6H_5N_3 \quad (114)$$

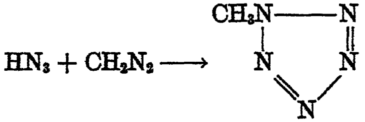
Diazonium salts may be converted to azides by treatment with hydroxylamine hydrochloride (110, 221, 318) or with sodium azide (257). By the use of this method, a great variety of aromatic azido compounds has been prepared, such as: $N_3C_6H_4OH$ (*o*-, *m*-, and *p*-) (119); $N_3C_6H_4N_3$ (*m*- and *p*-) (334, 120, 147); $N_3C_6H_4CHO$ (*p*-) (124); $N_3C_{10}H_6NO_2$ (1,2-; 1,4-; 1,5-; 1,8-; 2,5-; 2,8-) (120); $N_3C_6H_4I$, $N_3C_6H_4IO_2$ (115).

Phenylhydrazine reacts with nitrous acid or nitrosyl chloride to give a nitroso compound which immediately loses water, forming an azide (94). The reaction may be extended to the hydrazides of the acids (90, 89).

The simplest aliphatic azide, methyl azide, was first obtained by methylation of sodium azide with methyl sulfate (101).

$$2NaN_3 + (CH_3)_2SO_4 \rightarrow Na_2SO_4 + 2CH_3N_3$$

The same substance was obtained recently (266) in an attempt to prepare methylpentazole by the addition of diazomethane to hydrazoic acid, and Oliveri-Mandala believes that the methyl azide resulting from this reaction is due to the decomposition of the intermediate methylpentazole.



Forster and his collaborators (121, 122, 125, 126, 128, 129) prepared a large number of mono- and di-azido aliphatic esters, alcohols, aldehydes, ketones, and acids by treatment of the corresponding halogen compounds with sodium azide:

$$RX + NaN_3 \rightarrow RN_3 + NaX$$

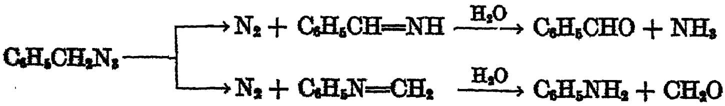
In their reactions the azides show a similarity to the aliphatic diazo compounds. A very common reaction consists in the loss of two nitrogen atoms and occurs when the substances are boiled with acids or bases. For example, phenyl azide is converted into *p*-aminophenol, and phenylhydroxylamine is probably an intermediate (146, 132).

$$C_6H_5N_3 + H_2O \rightarrow C_6H_5NHOH + N_2 \rightarrow p\text{-}HOC_6H_4NH_2$$

Azidoketones are decomposed in a similar manner, yielding imines (118a, 121, 121a).

$$RCOCH_2N_3 \rightarrow N_2 + RCOCH{=}NH$$

Benzyl azide was found to decompose in two ways (88) to give benzaldehyde and aniline, the latter product resulting from a rearrangement.



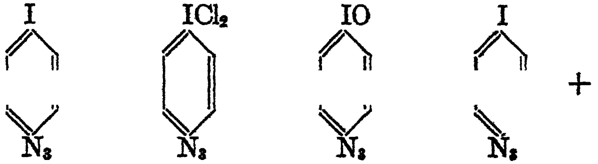
$$C_6H_5CH_2N_3 \rightarrow N_2 + C_6H_5CH{=}NH \xrightarrow{H_2O} C_6H_5CHO + NH_3$$

$$C_6H_5CH_2N_3 \rightarrow N_2 + C_6H_5N{=}CH_2 \xrightarrow{H_2O} C_6H_5NH_2 + CH_2O$$

Triphenylmethyl azide also decomposes with rearrangement and the final products are benzophenone and aniline (200).

$$(C_6H_5)_3CN_3 \longrightarrow N_2 + (C_6H_5)_2C{=}NC_6H_5 \xrightarrow{H_2O} (C_6H_5)_2CO + C_6H_5NH_2$$

The rearrangement is not general, however, for in some cases the azido group is surprisingly stable. Thus *o*-, *m*-, and *p*-iodophenyl azides do not react with alcoholic alkali, and the iodine atom may be successively transformed to the dichloride and then to the iodoso and iodoxy compounds without disturbing the azido group (115).

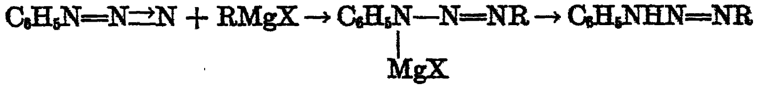


When ortho or para to a nitro group in the benzene ring, the azido group is removed as hydrazoic acid by boiling alcoholic alkali (256).

$$N_3C_6H_4NO_2 + 2KOH \rightarrow KOC_6H_4NO_2 + KN_3 + H_2O$$

But when the azido group is meta to the nitro group, this reaction does not occur. The same rule holds in the naphthalene series (120), only the 1,2-, 1,4-, and 2,1-nitroazidonaphthalenes hydrolyzing to give hydrazoic acid.

Both alkyl and aryl azido compounds are transformed into diazoamino compounds by action of Grignard reagents (96), and this reaction may be interpreted as a 1,3-addition:



$$C_6H_5N{=}N\stackrel{\rightarrow}{=}N + RMgX \rightarrow C_6H_5\underset{\displaystyle MgX}{\underset{|}{N}}{-}N{=}NR \rightarrow C_6H_5NHN{=}NR$$

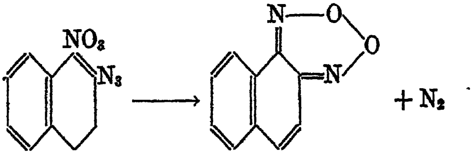
The same type of addition may be invoked to explain the reaction with hydrocyanic acid (387):

$$C_6H_5N{=}N\stackrel{\rightarrow}{=}N + HCN \rightarrow C_6H_5NHN{=}NCN$$

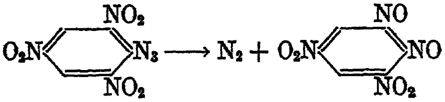
The *o*-nitrophenyl azides, when heated, lose a molecule of nitrogen, and dinitroso compounds result (388):

$$N_3C_6H_4NO_2 \rightarrow O{=}NC_6H_4N{=}O + N_2$$

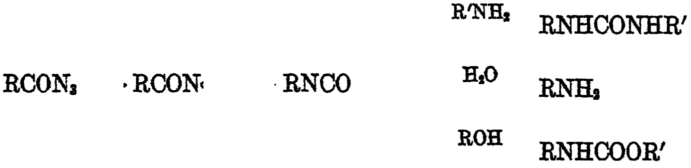
although Forster and Fierz (120), who obtained similar compounds in the naphthalene series, prefer to write them as dioxime peroxides.



However, Schrader (326) decided that the decomposition product of picryl azide was a nitroso compound:



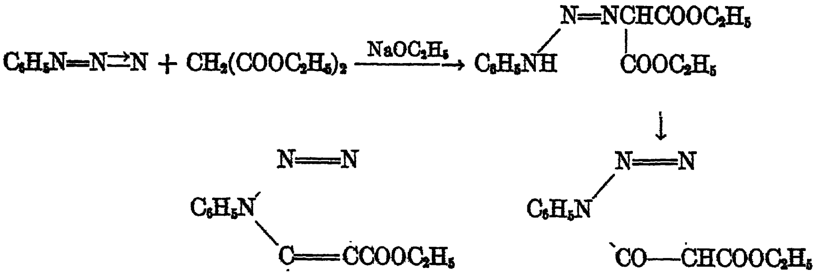
Acid azides undergo the well-known Curtius rearrangement (87), although the reaction is not entirely general, and compounds from which isocyanates cannot be formed behave abnormally (sulfonyl azides, etc.).



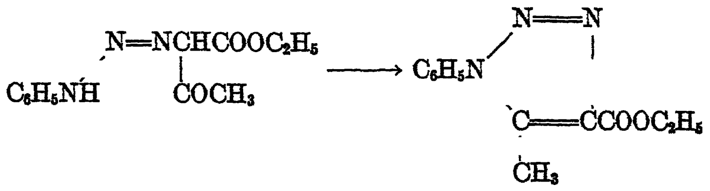
$$\mathrm{RCON_3} \qquad \cdot\,\mathrm{RCON} \qquad \cdot\,\mathrm{RNCO} \qquad \begin{array}{ll} \mathrm{R'NH_2} & \mathrm{RNHCONHR'} \\ \mathrm{H_2O} & \mathrm{RNH_2} \\ \mathrm{ROH} & \mathrm{RNHCOOR'} \end{array}$$

Lately the Curtius rearrangement has been developed by von Braun, Nelles, and others, and has become a convenient and useful method for the transformation of an acid or acid halide to an amine with loss of one carbon atom (327, 72, 250, 249, 251).

The azides undergo many reactions which involve ring closure, most of which may be considered as direct 1,3-additions. Phenyl azide condenses with many substances containing active methylene groups; the final products are 1,2,3-triazoles (95, 99).

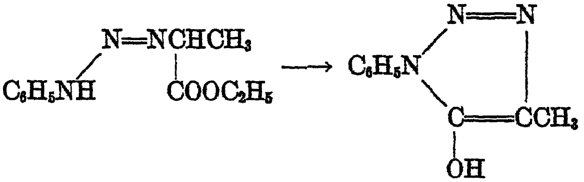


$C_6H_5N{=}N\rightleftarrows N + CH_3COCH_2COOC_2H_5 \longrightarrow$

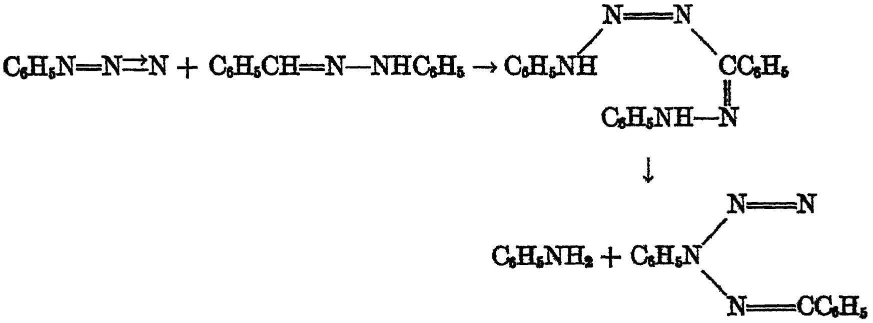


Even esters, such as ethyl acetate or ethyl propionate, will undergo this condensation.

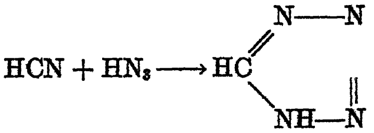
$C_6H_5N{=}N\rightleftarrows N + CH_3CH_2COOC_2H_5 \longrightarrow$

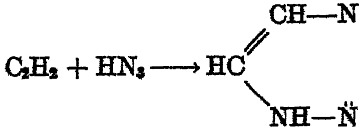


A similar reaction occurs between phenyl azide and some hydrazones (100).



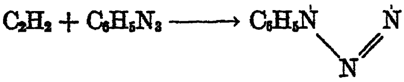
The addition of hydrazoic acid to hydrocyanic acid produces tetrazole (97), while triazole is obtained when hydrazoic acid adds to acetylene (127).

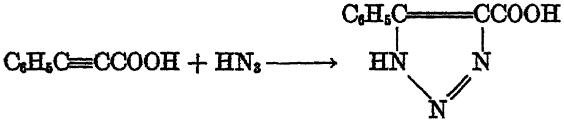




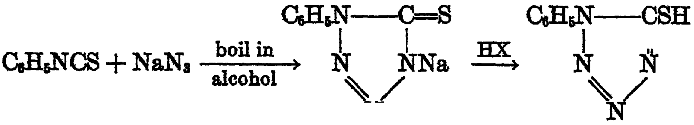
Since Forster and Newman prepared vinyl azide and found it to be a stable substance, it is evident that the reaction between acetylene and hydrazoic acid cannot involve a rearrangement of vinyl azide, but must involve a direct 1,3-addition of hydrazoic acid.

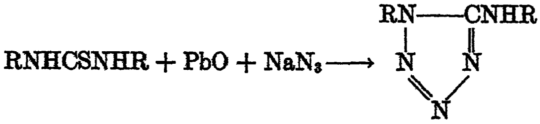
Similar reactions are those between phenyl azide and acetylene, and between hydrazoic acid and phenylpropiolic acid (240, 98, 268).



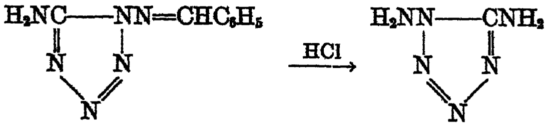


Many other reactions of the azides which lead to heterocyclic compounds may conveniently be formulated as direct 1,3-additions: thus

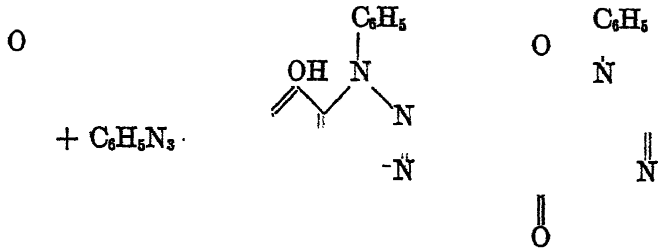

(350)

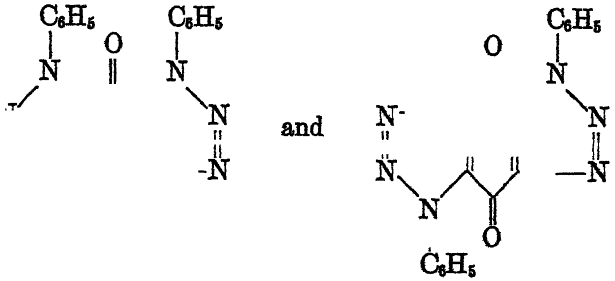

(348)

$H_2NNHCSNH_2 + NaN_3 + PbO + C_6H_5CHO \longrightarrow$

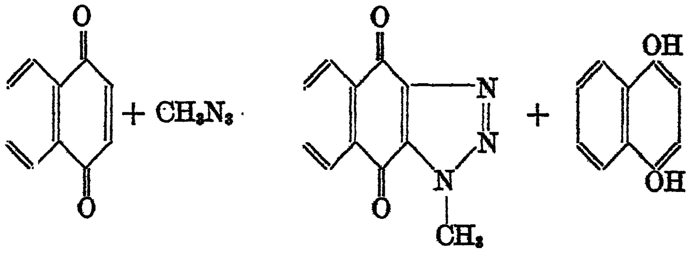

(349)

Phenyl azide reacts with quinones (386, 107, 106), adding to the double bond. In benzene at 60–65°C. benzoquinone and the azide react to give first the aziminohydroquinone, which may be oxidized by unchanged quinone to the aziminoquinone, and the latter may then react further:

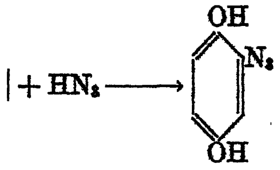


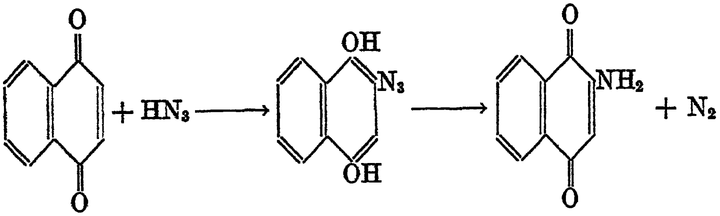


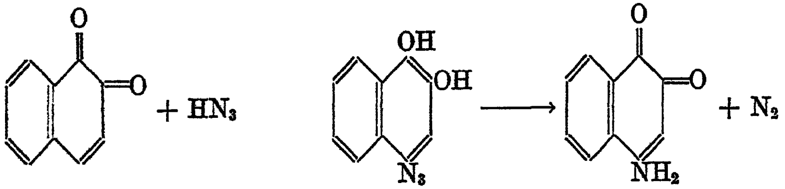
α-Naphthoquinone reacts in the same way with methyl azide (106):

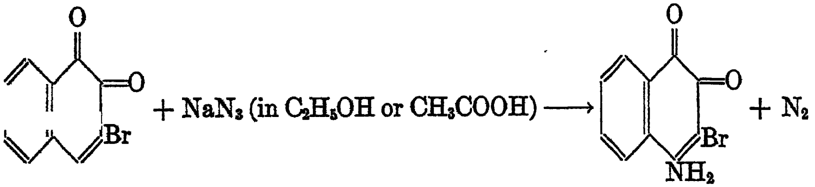


Hydrazoic acid, however, adds 1,4 to benzoquinone (267, 263) to give azidohydroquinone, and a similar reaction occurs with both α- and β-naphthoquinones (106), and also with 3-bromo-1,2-naphthoquinone.

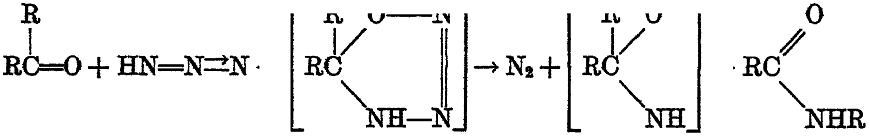




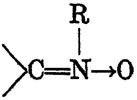




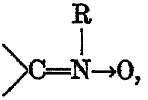
Hydrazoic acid reacts with carbonyl compounds in much the same fashion as diazomethane. The latter reagent produces methyl ketones from aldehydes and homologs from ketones, while hydrazoic acid produces amides, the product that would have been obtained by the Beckmann rearrangement of the oxime of the carbonyl compound (24). As the reaction with diazomethane may be formulated as involving an initial 1,3-addition, so may the reaction with hydrazoic acid:



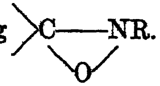
III. NITRONES: THE *N*-ETHERS OF THE OXIMES.



$$\overset{\displaystyle R}{\overset{|}{>C=N\rightarrow O}}$$

The name "nitrone" was coined by Pfeiffer (284) to designate substances having the linkage  $\overset{R}{\overset{|}{>C=N\rightarrow O}}$, because they behave like ketones in some respects. Pfeiffer had in mind the similarity between C=O and N→O in coining the name. It was rather unfortunate because, actually, it is the whole system, $\rangle C{=}\overset{|}{N}{\rightarrow}O$, which acts as a long carbonyl group and *not* the linkage N→O. This makes it very difficult to name individual compounds as nitrones; hence it is better to use the name "nitrone" for all classes of compounds containing the group $\rangle C{=}\overset{|}{N}{\rightarrow}O$, whether in open or closed chains, and to name the individual compounds in other ways.

The *N*-ethers of the oximes are the simplest nitrones; they are open-chain compounds. The nitrones behave in most of their reactions as carbonyl compounds, for the nitrone group $\rangle C{=}\overset{|}{N}{\rightarrow}O$ reacts much like a long carbonyl group with addition taking place at the ends of the system. The middle nitrogen atom does not take part in these addition reactions except to drop its valence from "5" to 3.

It is possible to write the nitrones as a three-membered ring 

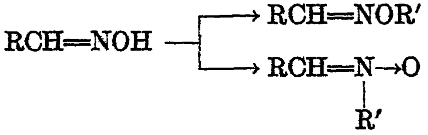
This was done for some time after the discovery of the *N*-ethers of the oximes and similar compounds. The three-membered ring formula is still used in some special cases (340, 134, 308), but the evidence against the three-membered ring is considerable and each new thorough study of compounds of this type makes it more apparent that they cannot be represented by a three-membered ring structure (12). No such ring structure as this has been proved to exist in any compound with certainty, and in many cases in which it has been assumed, as in the azoxy compounds, it has been shown to be incorrect. The spectrochemical results of Brady (59) and of v. Auwers and Ottens (30), the parachor studies of Sugden (351), and the color of the nitrones indicate that they do not contain a three-membered ring. Moreover, the three-membered ring does not suffice stereochemically; compounds containing such a structure should show optical activity, for the ring has an asymmetric carbon atom (177). Experiments directed toward the resolution of these *N*-ethers have failed (322, 215). Hence these *N*-ethers of the oximes must be *nitrones*.

Three methyl ethers and three benzyl ethers of benzaldoxime are known. Of these respectively, two are *O*-ethers and one is an *N*-ether, for with hydriodic acid the R group of the one (*N*-ether) appears as a primary amine, while from the other two (*O*-ethers) it appears as alkyl iodide. Since the *O*-ethers must be $C_6H_5CH{=}NOR$ (*syn* and *anti*), the *N*-ether must be $C_6H_5CH{=}\underset{\underset{R}{|}}{N}{\rightarrow}O$. Both *syn*- and *anti*-forms of benzaldoxime on alkylation give the *N*-ether plus one of the *O*-ethers (150a, 40, 138). Beckmann showed that the liquid α-benzaldoxime, alkylated with benzyl chloride, gave the *O*-ether, while the solid β-benzaldoxime gave the *N*-ether. Goldschmidt showed that α- and β-benzaldoxime each gave, with phenyl isocyanate, two isomers, $C_6H_5NHCO{-}ON{=}CHC_6H_5$, which were easily changed into each other. Hence the aldoximes must be stereoisomers and Beckmann's two ethers must be structural isomers. Later Beckmann showed that the β-benzaldoxime actually gave both *O*- and *N*-ethers on alkylation.

A. Preparation of the N-ethers of the oximes

1. Preparation from the oximes

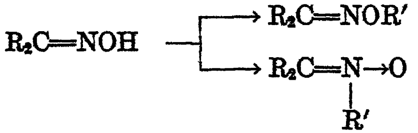
Aldoximes and ketoximes can be directly alkylated (though not arylated) and, according to the conditions, there result *O*-ethers, *N*-ethers, or mixtures of the two.



$$\mathrm{RCH{=}NOH} \begin{cases} \rightarrow \mathrm{RCH{=}NOR'} \\ \rightarrow \mathrm{RCH{=}\underset{\substack{|\\ R'}}{N}{\rightarrow}O} \end{cases}$$

O-ether of an aldoxime

N-ether of an aldoxime (nitrone)



$$\mathrm{R_2C{=}NOH} \begin{cases} \rightarrow \mathrm{R_2C{=}NOR'} \\ \rightarrow \mathrm{R_2C{=}\underset{\substack{|\\ R'}}{N}{\rightarrow}O} \end{cases}$$

O-ether of a ketoxime

N-ether of a ketoxime (nitrone)

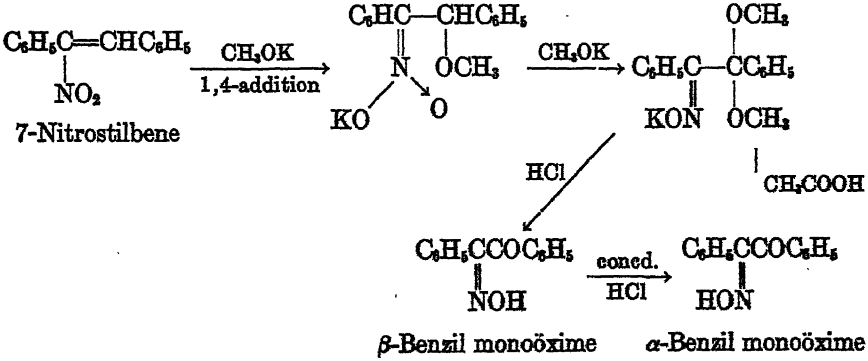
In general, the ketoximes are not as reactive toward alkylating (and other) reagents as are the aldoximes. The course taken by the alkylation of aldoximes and ketoximes depends to a great extent upon the experimental procedure and the nature of the alkyl group (135, 133, 282, 139–142, 220, 298, 166, 118, 60, 64, 66, 67). Methylation of benzophenone oxime in alkaline solution gives the *O*-ether (m.p. 60°C.) and the *N*-ether (m.p. 102°C.). These can be separated, since the nitrone is much less soluble in petroleum ether, or the nitrone hydrochloride may be precipitated from ether solution with gaseous hydrochloric acid (2).

The methyl ethers of the aldoximes have been most thoroughly investigated. The *syn*- and *anti*-aldoximes behave alike when their silver salts are treated with methyl iodide or when the oximes are treated with methyl iodide and silver oxide, the *O*-ethers resulting exclusively (215, 139–142, 60, 64, 66, 67). The same rule holds in the case of ketoximes when they are treated with alkyl iodides and silver oxide or when their silver salts are treated with alkyl halides (166, 2). In *alkaline* solution, however, the relationships are different, for in this case either RX or R_2SO_4 (acting upon the alkali salts of the oximes) gives a mixture of *O*- and *N*-ethers (298, 2, 319, 93, 148, 329, 68). The relative amounts of *O*- and *N*-ethers obtained in this way change with the nature of the oxime, especially with its dissociation constant, for the larger this is, the more of the *O*-ether results (60, 64, 66, 67); also, increasing the amount of alkali results in the formation of more *O*-ether (60, 64, 66, 67). When methyl sulfate or methyl iodide acts on aldoximes in the dark and in the absence of alkali, only the *N*-ether results (in the form of its salt (60, 64, 66, 67)).

Diazomethane usually methylates an aldoxime, giving the *O*-ether, but the stereoisomeric oximes may behave quite differently. The α-form usually reacts, while the β-form is inert (118). The ketoximes are usually inactive toward diazomethane (118).

The same procedures may be used to obtain ethers of 1,2-dioximes. The mono- or di-oximes with an alkyl iodide and sodium methoxide or, better, with an alkyl sulfate and sodium hydroxide (298, 29, 167, 113, 32, 69, 70, 356) give mixtures of *O*- and *N*-ethers. From the dioximes *O*,*O*-, *N*,*N*-, and *O*,*N*-ethers are possible. Alkylation with alkyl iodides and silver oxide in absolute ether (67, 112) gives exclusively *O*-ethers. Diazomethane apparently gives the *N*-ethers of α-diketone monoöximes, but the yields are poor and rearrangements often result (123, 118, 69, 70). The mono ethers of the dioximes can be made by two methods: by the action of 1 mole of R_2SO_4 upon the dioxime in the presence of alkali, or by the action of hydroxylamine upon the ethers of the monoöximes (69).

A method of preparing the monoöximes of 1,2-dicarbonyl compounds consists in the action of potassium hydroxide in methanol upon unsaturated nitro compounds. This reaction leads first to the oxime of the acetal of the 1,2-dicarbonyl compound and then to the monoöxime (229–233).

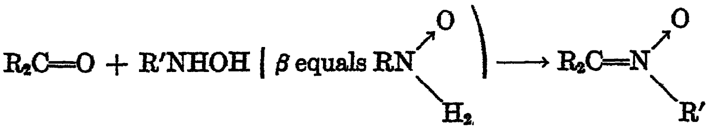


This method possesses the advantage that the position of the oxime group is known if the diketone is unsymmetrical.

2. Preparation from the aldehydes and ketones

The ethers are prepared from the aldehydes and ketones, by reaction with substituted (α- or β-) hydroxylamines.

$R_2C{=}O + H_2NOR'\ (\alpha) \longrightarrow R_2C{=}NOR'$ *O*-ether

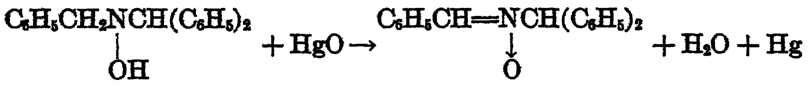


$$R_2C{=}O + R'NHOH \left|\ \beta \text{ equals } RN\begin{matrix}\nearrow O\\ \searrow H_2\end{matrix}\right) \longrightarrow R_2C{=}N\begin{matrix}\nearrow O\\ \searrow R'\end{matrix}$$

N-ether

α-Alkylhydroxylamines with *aldehydes* usually react smoothly to give the *O*-ethers, often both stereoisomers resulting, while the β-alkylhydroxylamines give the *N*-ethers. The reaction between ketones and α-substituted hydroxylamines has apparently not been studied very much, while the β-substituted hydroxylamines apparently do not react smoothly with ketones (60, 64, 66, 67, 43, 320).

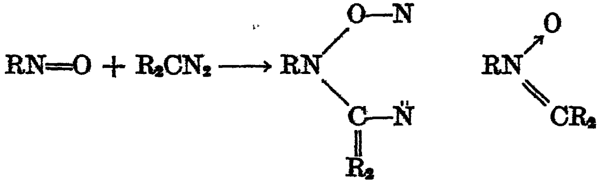
Oxidation of some *N*,*N*-dialkylhydroxylamines by mercuric oxide gives nitrones:



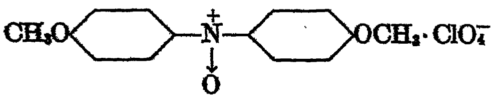
$$\underset{\displaystyle OH}{C_6H_5CH_2\underset{|}{N}CH(C_6H_5)_2} + HgO \rightarrow \underset{\displaystyle O}{C_6H_5CH{=}\underset{\downarrow}{N}CH(C_6H_5)_2} + H_2O + Hg \quad (2)$$

3. Preparation from nitroso compounds

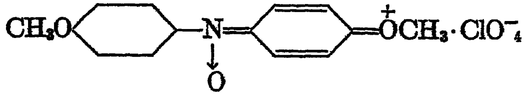
The action of aliphatic diazo compounds on nitroso compounds gives nitrones.



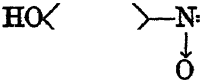
This probably involves a primary 1,3-addition of the nitroso group to the diazo compound and may be compared with the reaction between diazomethane and aldehydes to give methyl ketones (345, 274). Some complicated nitrones have been obtained by K. Meyer (238, 239, 237) and his students by the action of nitric acid upon phenol ethers. The reaction produces an intensely colored solution and, by adding perchloric acid to this, Meyer succeeded in isolating crystalline, colored salts which analyzed for the perchlorate of a nitrone.

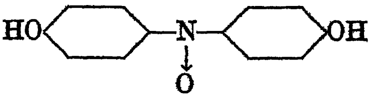


or

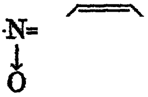


When reduced, this product gave *p,p′*-dimethoxydiphenylamine. Treatment with alkali, pyridine, sodium iodide, or zinc dust decomposed the perchlorate, giving some of the radical, dianisylnitrogen oxide, $(CH_3OC_6H_4)_2N{\rightarrow}O$. This radical, with bromine or mineral acids, again gave the colored salt. Phenol itself will react in the same manner as anisole. The colored salts obtained are derived from indophenol oxide (I). On mild reduction the product is *p,p′*-dihydroxydiphenylnitrogen oxide (II). These quinoid colored salts are the oxy derivatives of the orange-yellow quinone anil oxide (III), prepared by Wieland and Roth.



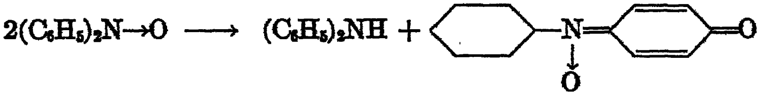


II



III

If an ethereal solution of diphenylnitrogen oxide is shaken with hydrochloric acid, disproportionation occurs to diphenylamine and the quinone anil oxide (III) (150, 238, 239, 237, 380):



B. Properties of the oxime ethers (298, 67, 148, 329, 68, 62, 65, 66)

1. The *O*-ethers

These ethers are usually quite stable toward hydrolyzing agents. Boiling with aqueous or alcoholic hydrochloric or hydrobromic acids, with 60 per cent sulfuric acid, or with 2 *N* sodium hydroxide produces no change. They are weaker bases than the oximes themselves, forming no hydrochlorides or chloroplatinates (thus differing from the *N*-ethers which form both). They give no metallic salts with bases, nor do they form any addition compounds. With fuming hydrochloric acid they are hydrolyzed, giving the carbonyl compound and the hydrochloride of the α-substituted hydroxylamine.

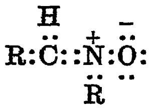
The oximes themselves, especially the aldoximes, give stable salts with bases and also with strong acids, although the latter are easily hydrolyzed. The *N*-ethers are more basic than the oximes, while the *O*-ethers are less basic, giving no salts at all, although there is not complete agreement on this point. The *O*-ethers do not undergo the Beckmann rearrangement.

2. The *N*-ethers

These ethers are very reactive substances, in which the basicity of the nitrogen is greater than that in the oximes themselves. They hydrolyze more readily (to $R_2C{=}O + RNHOH$) than *O*-ethers, and they form many addition products which *O*-ethers do not. They form salts with acids, and although these salts are easily hydrolyzed by water, they are more stable than the salts formed from the oximes and acids. The *N*-ethers are very easily hydrolyzed. Cold concentrated hydrochloric acid hydrolyzes them almost instantly to the carbonyl compound and the *N*-substituted hydroxylamine. Dilute acid acts more slowly, but very rapidly if warmed. Alkali also hydrolyzes the *N*-ethers quickly. The ketoxime *N*-ethers are more rapidly attacked by alkali than are the aldoxime *N*-ethers.

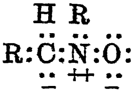
The *N*-ethers form well-defined, fairly stable chloroplatinates and other complex salts, and they show great additive power toward many other reagents. They readily form hydrates (321) and other addition products, e.g., with sodium iodide and calcium chloride, hence one must be careful in making the *N*-ethers to avoid these addition products. The ketoxime *N*-ethers are known to form addition products with oximes (329, 3), with water, hydroquinone, and with phenyl isocyanate (329). These addition products are strongly dissociated in solution.

The electronic structure of the nitrones is



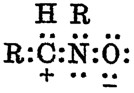
$$\mathrm{R}{:}\overset{\mathrm{H}}{\overset{\cdot\cdot}{\mathrm{C}}}{::}\underset{\mathrm{R}}{\underset{\cdot\cdot}{\overset{+}{\mathrm{N}}}}{:}\underset{\cdot\cdot}{\overset{-}{\overset{\cdot\cdot}{\mathrm{O}}}}{:}$$

for the stable form which can resonate between the reactive forms



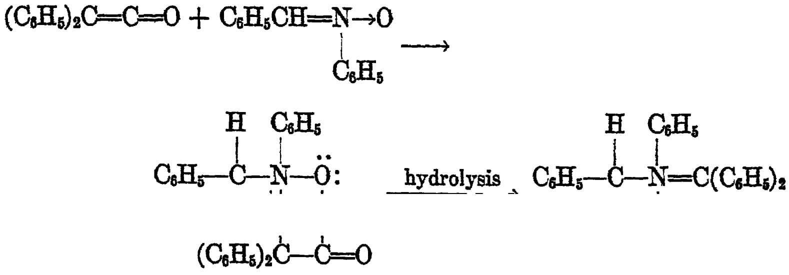
$$\mathrm{R}{:}\underset{\overset{\cdot\cdot}{-}}{\overset{\mathrm{H}}{\overset{\cdot\cdot}{\mathrm{C}}}}{:}\underset{++}{\overset{\mathrm{R}}{\overset{\cdot\cdot}{\mathrm{N}}}}{:}\underset{\overset{\cdot\cdot}{-}}{\overset{\cdot\cdot}{\mathrm{O}}}{:}$$

and



$$\mathrm{R}{:}\underset{+}{\overset{\mathrm{H}}{\overset{\cdot\cdot}{\mathrm{C}}}}{:}\underset{\cdot\cdot}{\overset{\mathrm{R}}{\overset{\cdot\cdot}{\mathrm{N}}}}{:}\underset{\overset{\cdot\cdot}{-}}{\overset{\cdot\cdot}{\mathrm{O}}}{:}$$

Most reactions of nitrones involve the second of these reactive forms, and may be interpreted as 1,3-additions, although addition of ketenes probably involves the first of the active forms. Thus (345):

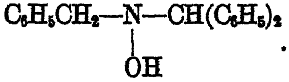


$$(C_6H_5)_2C{=}C{=}O + C_6H_5CH{=}\underset{\displaystyle C_6H_5}{\underset{|}{N}}{\rightarrow}O \longrightarrow$$

$$\begin{matrix} & \overset{\displaystyle H}{|} & \overset{\displaystyle C_6H_5}{|} & \\ C_6H_5— & C & —N— & \ddot{O}\!: \\ & (C_6H_5)_2\dot{C} & — & \dot{C}{=}O \end{matrix} \xrightarrow{\text{hydrolysis}} C_6H_5—\overset{\displaystyle H}{\overset{|}{C}}—\overset{\displaystyle C_6H_5}{\overset{|}{N}}{=}C(C_6H_5)_2$$

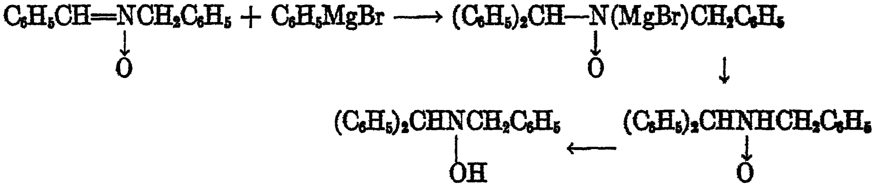
Triphenyl-*N*-phenyl-
nitrene[2]

Grignard reagents, alcohols, acetyl chloride, acetic anhydride, and isocyanates all react with nitrones according to the second active form (12, 59, 215, 329, 68, 29, 32, 65, 66, 321, 352, 61, 102, 70). In reactions between any of these substances and nitrones, the addenda are found attached to the ends of the unsaturated 1,3-system whenever the primary product is stable enough to be examined chemically. Thus, in the addition of phenylmagnesium bromide to the *N*-benzyl ether of benzaldoxime, Angeli obtained benzylbenzhydrylhydroxylamine,



$$C_6H_5CH_2—\underset{\displaystyle OH}{\underset{|}{N}}—CH(C_6H_5)_2.$$

To account for this, Angeli assumed addition to the 1,2-system, C=N. Thus



$$C_6H_5CH{=}\underset{\displaystyle O}{\underset{\downarrow}{N}}CH_2C_6H_5 + C_6H_5MgBr \longrightarrow (C_6H_5)_2CH—\underset{\displaystyle O}{\underset{\downarrow}{N}}(MgBr)CH_2C_6H_5$$

$$\downarrow$$

$$(C_6H_5)_2CH\underset{\displaystyle OH}{\underset{|}{N}}CH_2C_6H_5 \longleftarrow (C_6H_5)_2CH\underset{\displaystyle O}{\underset{\downarrow}{N}}HCH_2C_6H_5$$

While it is possible to account for the structures of the addition products obtained with alcohols, water, and acetic acid by means of this mechanism, the addition of acid chlorides, anhydrides, and phenyl isocyanate cannot be so interpreted without assuming a migration of groups such as acyl or similar groups which do not migrate readily. It is therefore much more likely that the first addition is a direct 1,3-addition, and the addition of water, alcohols, and acids also can be readily interpreted in this way.

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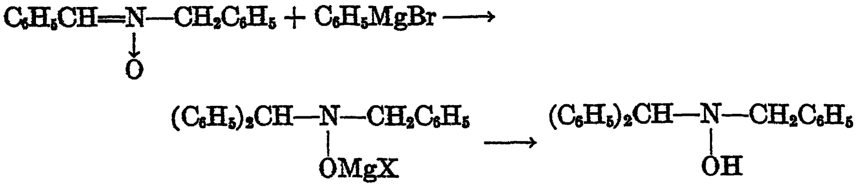
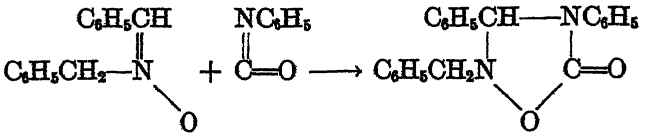
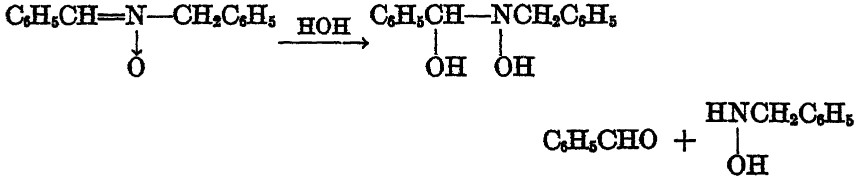
[2] See the footnote on page 267 regarding the recent evidence that the nitrenes are derivatives of ethyleneimine, i.e., are ring compounds.

Thus, for the addition of phenylmagnesium bromide, phenyl isocyanate, and HX compounds the following reactions can be written, and in the case of phenyl isocyanate a most unusual rearrangement would have to be involved in order to obtain the product by a primary 1,2-addition (150).



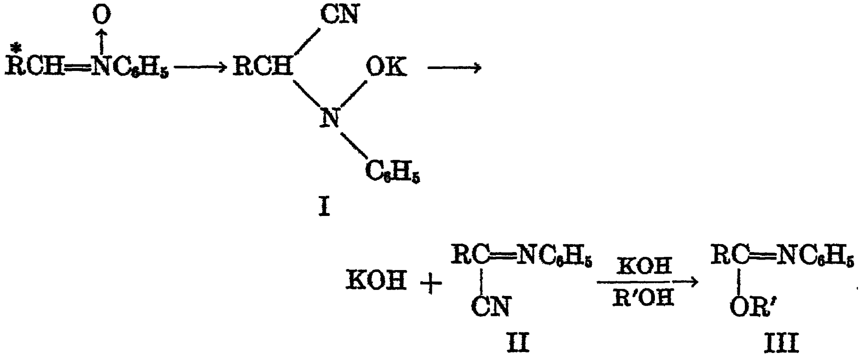
$$C_6H_5CH{=}\underset{\substack{\downarrow\\ O}}{N}{-}CH_2C_6H_5 + C_6H_5MgBr \longrightarrow (C_6H_5)_2CH{-}\underset{\substack{|\\ OMgX}}{N}{-}CH_2C_6H_5 \longrightarrow (C_6H_5)_2CH{-}\underset{\substack{|\\ OH}}{N}{-}CH_2C_6H_5$$





$$C_6H_5CH{=}\underset{\substack{\downarrow\\ O}}{N}{-}CH_2C_6H_5 \xrightarrow{HOH} C_6H_5\underset{\substack{|\\ OH}}{CH}{-}\underset{\substack{|\\ OH}}{N}CH_2C_6H_5 \qquad C_6H_5CHO + \underset{\substack{|\\ OH}}{HN}CH_2C_6H_5$$

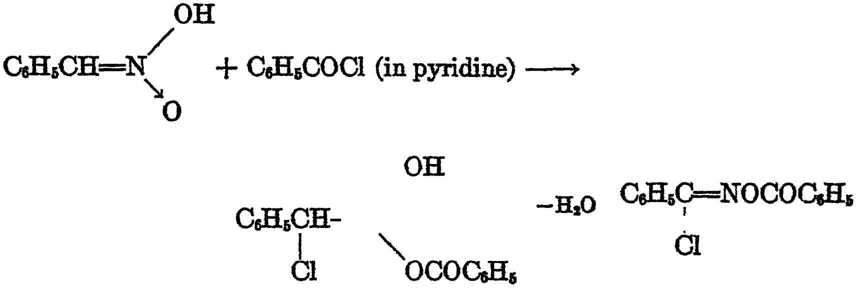
In two recent papers Bellavita (46) has examined the action of potassium cyanide upon alcoholic solutions of *o*-, *m*-, and *p*-nitrophenyl-*N*-phenylnitrones. The reaction apparently involves a primary 1,3-addition of the cyanide, leading first to I (not isolated) and then to II. The latter reacts with the solvent to give III.



* (R = *o*-, *m*-, or *p*-nitrophenyl).

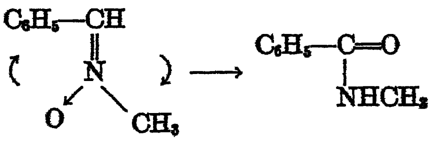
II can be isolated only when exactly equimolecular proportions of nitrone and potassium cyanide are used; otherwise the reaction leads directly to III, the yields of which are excellent.

The reaction between benzoyl chloride and *aci*-phenylnitromethane (379), which is also a nitrone, may be written as follows:

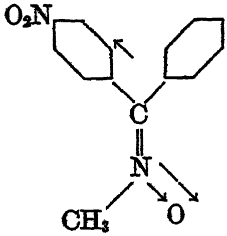


While the *N*-ethers of the aldoximes are known in rather large numbers (321), they almost never show the *cis-trans* isomerism theoretically possible, in spite of numerous statements to the contrary (220, 67, 66, 321, 130, 360, 143, 44). In only one case among the *N*-ethers of the aldoximes is *cis-trans* isomerism established with any certainty, and this case comprises the two *N*-ethers from 3-amino-2,6-dichlorobenzaldehyde and *N*-methylhydroxylamine (234). In the case of the *N*-ethers of ketoximes, isomeric *N*-ethers are known in two instances: 4-nitrobenzophenone *N*-methyl ether (68, 352) and 4-methylbenzophenone *N*-methyl ether (329).

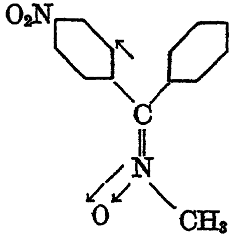
In contrast to the *O*-ethers, the *N*-ethers undergo the Beckmann rearrangement, the best reagent being acetic anhydride. Phosphorus pentachloride and acid chlorides do not react very smoothly (67, 63, 42). If the Beckmann rearrangement of the *N*-ethers is a *trans* rearrangement, then the *N*-ethers of the aldoximes belong to the *β*-series, for benzaldoxime *N*-methyl ether gives *N*-methylbenzamide (63).



One has to be careful in determining the configurations of the *N*-ethers in this way, for the *α*-aldoximes themselves often change into the *β*-form and then undergo the rearrangement, and since there is no other independent method to fix the configuration of the *N*-ethers, it can be done only provisionally. Lately measurements of the dipole moments have indicated that the *N*-ethers are of the β(*anti*)-form (352). Because the oximes are strongly associated in solution, dipole moments are difficult to determine, but the *N*-ethers of the oximes can be handled very well. The data for the *N*-methyl ethers of 4-nitrobenzophenone oxime show the configuration to be as follows:

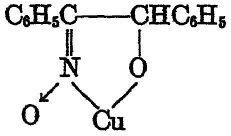


N-ether of the β-oxime (*anti*)
$\mu = 1.09 \times 10^{-18}$



N-ether of the α-oxime (*syn*)
$\mu = 6.60 \times 10^{-18}$

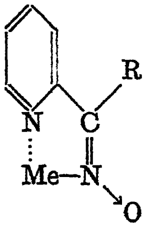
Many oximes form rather stable salts with the heavy metals; this is especially true when the metal can chelate or react in some other way with another group in the molecule. When this is possible, one form of the salt will always be much more stable than the other, and the more stable form is the one in which the N→O group is *anti* to the chelating or reacting position. These salts are derivatives of the (tautomeric) nitrone form of the oxime (285). Thus one can draw conclusions as to the configuration of some oximes from the ease with which they form complex salts and from the properties of the salts. α-Benzoin oxime gives a deep green, stable, copper salt (105) which is insoluble in acetic acid or ammonia. If this is a derivative of the nitrone form of the oxime, then the *anti* configuration for α-benzoin oxime is indicated, a result which agrees with the configuration as determined by other methods.



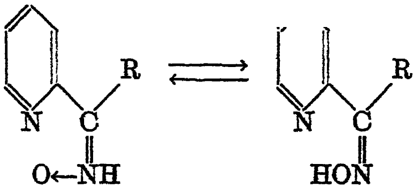
β-Benzoin oxime therefore should not form such a stable salt as this; actually it gives a gray-brown copper compound which is soluble in acetic acid or ammonia.

The tendency to form complex heavy-metal salts is less in the case of ketoximes than aldoximes, unless there is the possibility of forming inner complexes (chelation, etc.). Then one form will, and the other will not, give the heavy-metal complex; the form that reacts is the one with the

N-oxide form *anti* to the chelating or reacting position (131). Thus compound I would give a complex salt, while compound II would not.

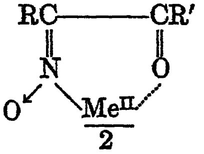


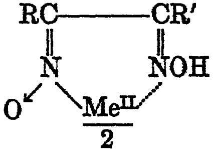
I



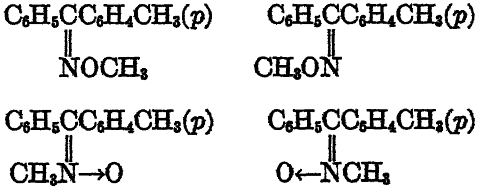
II

In the case of the monoöximes of aromatic and aromatic-aliphatic 1,2-diketones only the *anti*-forms give stable heavy-metal salts, while the *syn*-forms do not react. According to Pfeiffer these have the structure of nitrones; the same holds for the stable salts of the *anti*-dioximes (38, 39, 82, 159, 197, 199, 242, 290, 353, 354, 360a, 367).





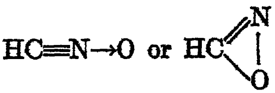
Semper and Lichtenstadt isolated the four isomeric ethers of phenyl *p*-tolyl ketoxime by methylating both the *syn*- and *anti*-oximes in alkaline solution with dimethyl sulfate (329).



$$\begin{array}{cc} C_6H_5CC_6H_4CH_3(p) & C_6H_5CC_6H_4CH_3(p) \\ \| & \| \\ NOCH_3 & CH_3ON \\ \\ C_6H_5CC_6H_4CH_3(p) & C_6H_5CC_6H_4CH_3(p) \\ \| & \| \\ CH_3N\rightarrow O & O\leftarrow NCH_3 \end{array}$$

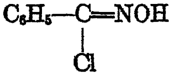
IV. THE NITRILE OXIDES: $RC\equiv N\rightarrow O$ (368)

The nitrile oxides were first made by Wieland (369), who has done most of the work on them. They, like the nitrones, can also be written in the form of a three-membered ring. The first member of the series, formonitrile oxide,



is the fourth known compound containing one atom each of carbon, hydrogen, oxygen, and nitrogen, and is isomeric with cyanic, isocyanic, and fulminic acids. In fact, formonitrile oxide was first thought to be fulminic acid; it is, however, different from fulminic acid, although it easily rearranges into an explosive substance which is perhaps fulminic acid.

The first observation on compounds of the nitrile oxide class was made by Werner and Buss (364), who found that the chloride of benzohydroxamic acid,



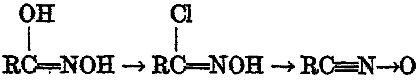
$$C_6H_5\text{—}\underset{\displaystyle Cl}{\underset{|}{C}}\text{=}NOH$$

when treated with sodium carbonate, lost the elements of hydrochloric acid and gave an oil of penetrating odor which rather quickly dimerized to the known diphenylglyoxime peroxide. Since the oil was hydrolyzed by concentrated hydrochloric acid to benzoic acid and hydroxylamine, it was regarded as benzonitrile oxide, $C_6H_5C\equiv N\rightarrow O$. In 1907 Wieland took up the study of this substance (369). He succeeded in isolating the pure, crystalline substance and showing that it was monomolecular. It was not as reactive as Wieland expected a substance of the structure

$$C_6H_5C\equiv N\rightarrow O$$

to be and therefore he used the ring formula,

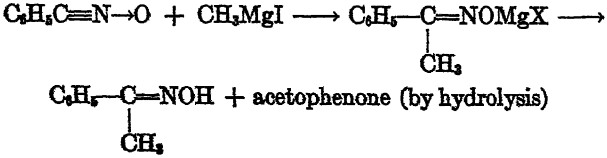
Almost the only method for the preparation of nitrile oxides consists in the action of mild alkalies on the hydroxamic acid chlorides:



$$R\overset{\displaystyle OH}{\overset{|}{C}}\text{=}NOH \rightarrow R\overset{\displaystyle Cl}{\overset{|}{C}}\text{=}NOH \rightarrow RC\equiv N\rightarrow O$$

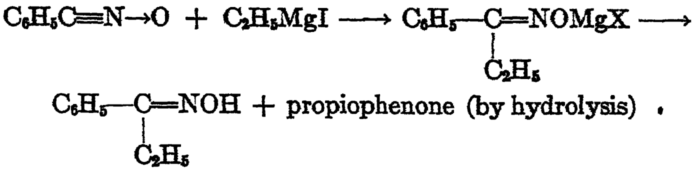
and only a few of these substances are known, although they are very likely intermediates in several transformations involving the hydroxamic acids, nitrolic acids, etc. (368, 371, 374–378, 379a, 381).

The nitrile oxides contain a 1,3-system and with Grignard reagents the mode of addition is probably 1,3. The products are ketoximes (369):



$$C_6H_5C\equiv N\rightarrow O + CH_3MgI \longrightarrow C_6H_5\text{—}\underset{\displaystyle CH_3}{\underset{|}{C}}\text{=}NOMgX \longrightarrow$$

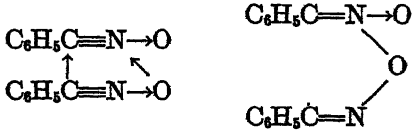
$$C_6H_5\text{—}\underset{\displaystyle CH_3}{\underset{|}{C}}\text{=}NOH + \text{acetophenone (by hydrolysis)}$$



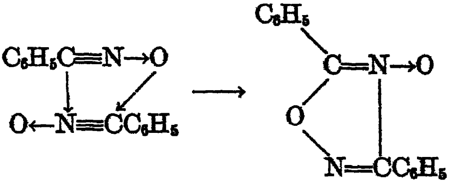
$$C_6H_5C\equiv N\rightarrow O + C_2H_5MgI \longrightarrow C_6H_5-\underset{C_2H_5}{\underset{|}{C}}=NOMgX \longrightarrow C_6H_5-\underset{C_2H_5}{\underset{|}{C}}=NOH + \text{propiophenone (by hydrolysis)}$$

On reduction benzonitrile oxide gives benzonitrile. This could be interpreted as removal of oxygen or as a 1,3-addition of hydrogen to give $C_6H_5CH{=}NOH$, which under the conditions of the experiment might behave as it does in the Beckmann rearrangement, giving benzonitrile.

In neutral or alkaline solution the nitrile oxides polymerize to the "glyoxime peroxides" (furoxans) (I), one molecule acting as a 1,3-system and the other as a 1,2-system, while in the presence of hydrochloric acid (or when the benzohydroxamic acid chloride spontaneously decomposes) the addition takes place in the inverse sense, giving the oxazoximes (II).

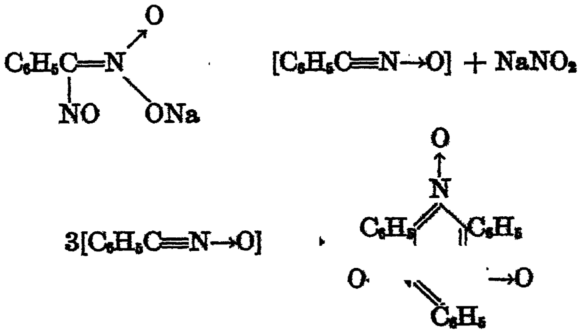


(I)



II

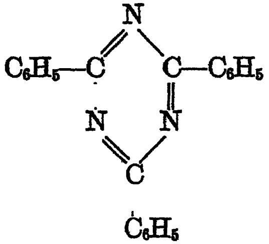
The furoxans and the oxazoximes both contain 1,3-systems, but benzonitrile oxide can (perhaps) polymerize in other ways. Thus, the sodium salt of benzonitrolic acid decomposes spontaneously to give a compound known as "tribenzonitrile oxide," and benzonitrile oxide, perhaps, may be an intermediate in this process.



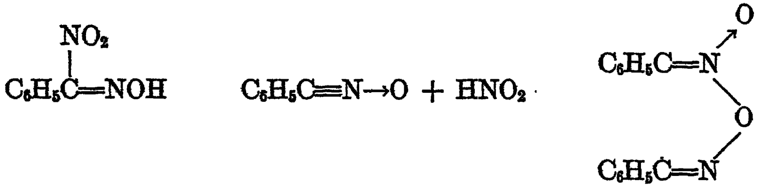
This is a reversible polymerization, while that to the furoxans and oxazoximes is not reversible. Thus, when the tribenzonitrile oxide is heated in indifferent solvents phenyl isocyanate is formed, and this substance can also be obtained by heating benzonitrile oxide.

$$\text{Trimer} \rightarrow C_6H_5C{\equiv}N{\rightarrow}O \rightarrow C_6H_5N{=}C{=}O$$

The above polymerization is similar to the polymerization of benzonitrile to give kyaphenine,

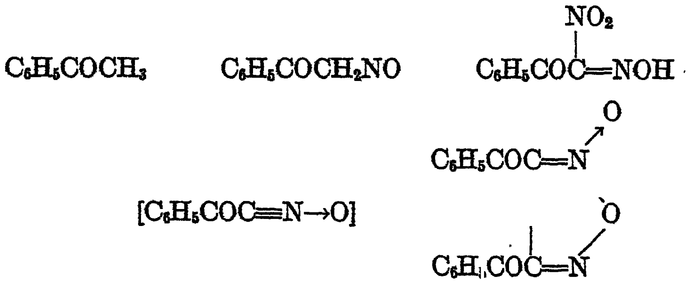


When the free benzonitrolic acid decomposes it gives the nitrile oxide, which then polymerizes to the glyoxime peroxide (furoxan):



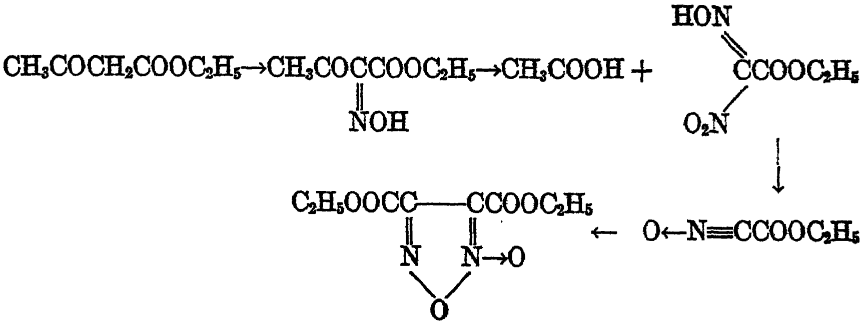
$C_6H_5C(NO_2){=}NOH \qquad C_6H_5C{\equiv}N{\rightarrow}O + HNO_2$

This reaction explains very well the behavior of acetophenone toward fuming nitric acid, a reaction which leads to "dibenzoylglyoxime peroxide" ("diphenyldinitrosacyl") (162):



$C_6H_5COCH_3 \qquad C_6H_5COCH_2NO \qquad C_6H_5COC(NO_2){=}NOH \qquad [C_6H_5COC{\equiv}N{\rightarrow}O]$

The similar transformation of acetoacetic ester into "glyoxime peroxide diester" with fuming nitric acid may be explained in the same way (301, 173):

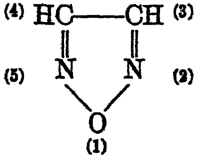


"Glyoxime peroxide di-ester"

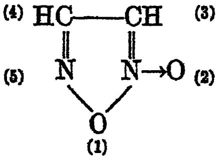
V. FURO-α,α'-DIAZOLES: FURAZANS AND FUROXANS

A. *Furazans*

Furazans contain the heterocyclic system (I); their *N*-oxides are furoxans (II).



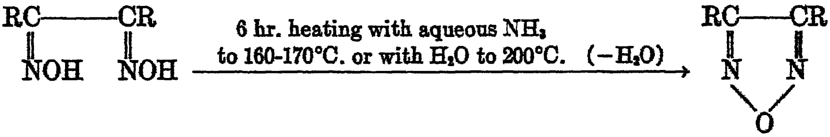
I



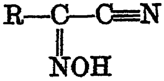
II

The latter contain the 1,3-nitrone system and are the "glyoxime peroxides." The compounds in which these ring systems occur are related to the acyclic dioximes.

The furazans are obtained by elimination of water from α-dioximes (383).

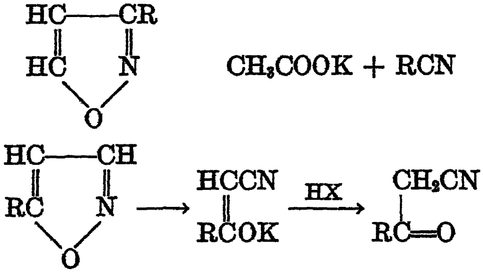

RC——CR
NOH NOH
6 hr. heating with aqueous NH₃
to 160-170°C. or with H₂O to 200°C. (−H₂O)
RC——CR
N N
O

The furazans can be regarded as isoxazoles with one CH group replaced by N, and the two classes of heterocycles show similarities in chemical properties. The furoxans and the isoxazoles show analogous behavior toward sodium hydroxide and sodium ethoxide; depending upon the presence or absence of substituents in certain positions, the ring either opens or is stable. If only one substituent is present on the carbon atoms, alkali converts furazans to oxime nitriles,

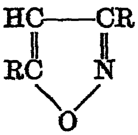


$$R-\underset{\underset{NOH}{\|}}{C}-C\equiv N$$

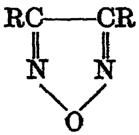
a reaction similar to that shown by monosubstituted isoxazoles:



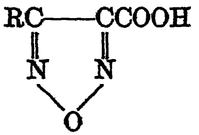
When two carbon atoms of either system carry substituents (I, II), the compounds are stable to alkali, and can even be oxidized by permanganate to the acids such as compound III.



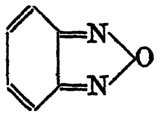
I



II



III



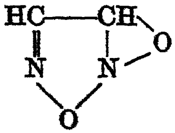
IV

Benzofurazans (IV) are obtained from the dioximes of *o*-quinones.

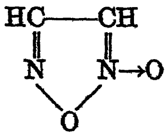
B. Furoxans

Dioximes can also be dehydrogenated; the products are "glyoxime peroxides" which Wieland (370) has shown to be, in the majority of cases, not true peroxides but furoxans. Most of them show no great oxidizing power but they do react with phosphorus pentachloride with or without a solvent (toluene, etc.) to give furazans, phosphorus oxychloride, and chlorine (this reaction of nitrones with phosphorus pentachloride to give phosphorus oxychloride, chlorine, and the desoxynitrone is a very general reaction of nitrones).

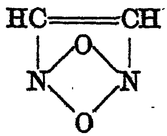
The furoxans can be written structurally in three ways (V, VI, and VII).



V



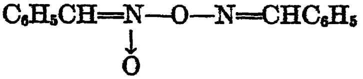
VI



VII

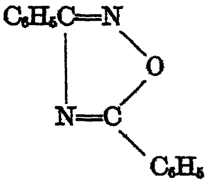
Wieland originally preferred formula V, Forster and Barker (116) and Green and Rowe (144) preferred formula VII, but in view of the work of Angeli (9) on the azoxy compounds formula VI is now preferred by most chemists.

Monoöximes can also be dehydrogenated to "peroxides," both the α- and β-aldoximes giving the same product. Whether these are true peroxides, such as $C_6H_5CH{=}N{-}O{-}O{-}N{=}CHC_6H_5$, or are open-chain furoxans,



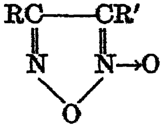
$$C_6H_5CH{=}\underset{\substack{\downarrow \\ O}}{N}{-}O{-}N{=}CHC_6H_5$$

is not known. As by-products in the oxidation of aldoximes there result azoximes (83, 45, 36, 41, 289, 296, 305):



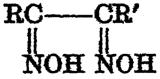
The glyoxime peroxides are formed by the mild oxidation of 1,2-dioximes (325) with potassium ferricyanide in alkaline solution (28, 198), nitrogen dioxide in ether (294), dilute nitric acid, bromine in dilute sulfuric acid, and sodium hypochlorite (294). Some dioximes, however, are not oxidized to peroxides by these reagents (294).

In the purely aromatic series the oxidation products are furoxans (372, 382).



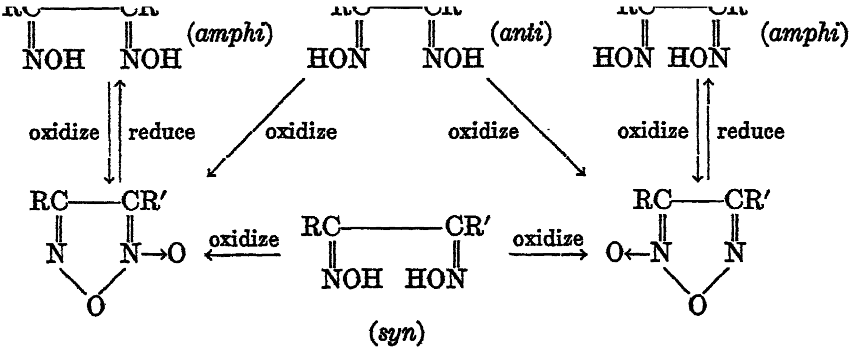
The peroxides of the *o*-quinone dioximes, however, are not furoxans, for they are symmetrical and they do not react with phosphorus pentachloride (116, 294, 372, 120, 145, 293, 196, 10, 48, 176, 25).

When, in the aromatic dioxime,

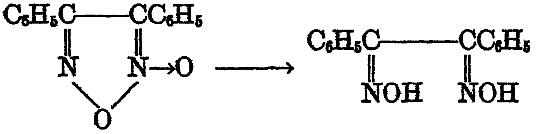


$$\underset{\substack{\| \\ NOH}}{RC}{-\!\!-}\underset{\substack{\| \\ NOH}}{CR'}$$

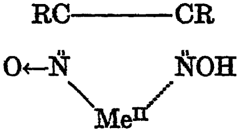
$R = R'$, one furoxan results (28, 103, 294, 372). When $R \neq R'$, two furoxans result (175, 231, 233). The oxygen is eliminated from all of these by the action of phosphorus pentachloride, and the corresponding furazans result (382). The furoxan formula implies that oxidation of the *anti-* and *syn*-dioximes involves a steric rearrangement, for the furoxans on reduction *always* give the *amphi*-oximes. This agrees with the fact that unsymmetrical dioximes give mixtures of the two possible furoxans, while each of the two *amphi*-oximes gives only one furoxan, and on reduction each furoxan gives the original *amphi*-oxime from which it came; thus



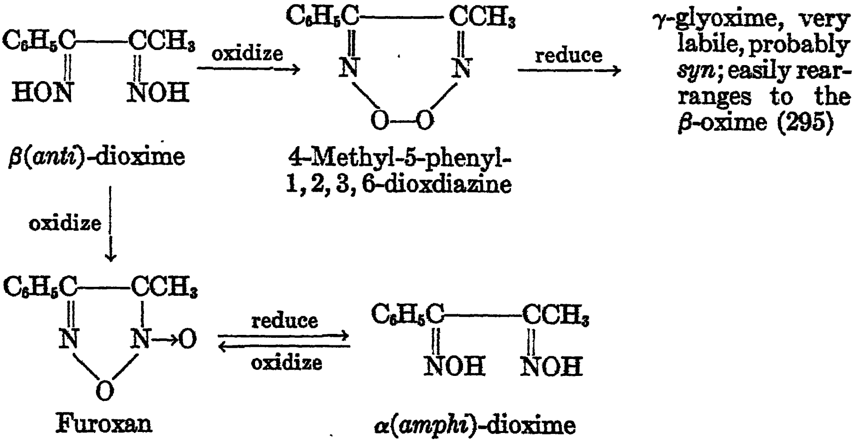
All three benzil dioximes give the same peroxide, which is a furoxan; on reduction it gives only the *amphi*-dioxime (4, 5, 370):



The *anti*-dioximes give stable heavy-metal salts,



The relationships are not so simple in the aliphatic-aromatic series of dioximes. Sometimes in this series only two oximes are known, one *anti* and one *amphi*. The α-form (*amphi*) on oxidation gives a furoxan which on reduction gives the same *amphi*-dioxime again (291, 294). The β-form (*anti*) sometimes gives two oxidation products. One is the furoxan, the same one which resulted from the oxidation of the *amphi*-dioxime; the other oxidation product is an entirely different substance, a dioxdiazine, apparently a true peroxide (241, 291, 292, 297, 299, 300). Thus



γ-glyoxime, very labile, probably *syn*; easily rearranges to the β-oxime (295)

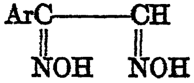
β(*anti*)-dioxime

4-Methyl-5-phenyl-1,2,3,6-dioxdiazine

Furoxan

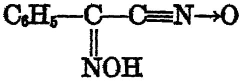
α(*amphi*)-dioxime

The aryl glyoximes of the type



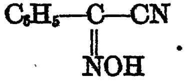
$$\begin{array}{ccc}\mathrm{ArC} & - & \mathrm{CH}\\ \| & & \| \\ \mathrm{NOH} & & \mathrm{NOH}\end{array}$$

behave still differently. The α(*amphi*)-form on oxidation gives *no cyclic* compound, but an oxide of an aroyl cyanide (295),



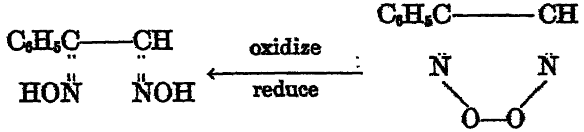
$$\begin{array}{l}\mathrm{C_6H_5{-}C{-}C{\equiv}N{\rightarrow}O}\\ \qquad\ \ \|\\ \qquad\mathrm{NOH}\end{array}$$

which on reduction gives the aroyl cyanide oxime,



$$\begin{array}{l}\mathrm{C_6H_5{-}C{-}CN}\\ \qquad\ \ \|\\ \qquad\mathrm{NOH}\end{array}.$$

The β(*anti*)-form also gives only one oxidation product; it is a dioxdiazine, and on reduction it gives the β-dioxime.



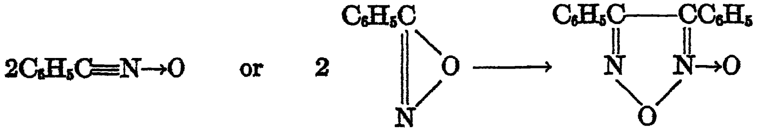
β-Phenylglyoxime

Reduction should give the *syn*-dioxime, and probably does so at first, but it is so unstable that it changes into the *anti*(β)-form at once.

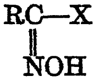
In the purely aliphatic series the structure of the "peroxides" is not known with certainty, but they are probably dioxdiazines.

1. Other preparations of furoxans

(*a*) By spontaneous, rather easy rearrangement of nitrile oxides (369).

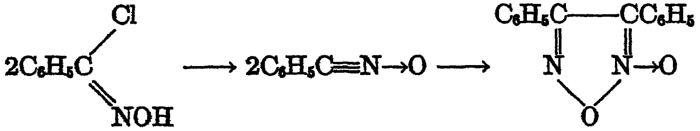


Because of this, furoxans often result by rearrangement of the hydroxamic acids and their derivatives,

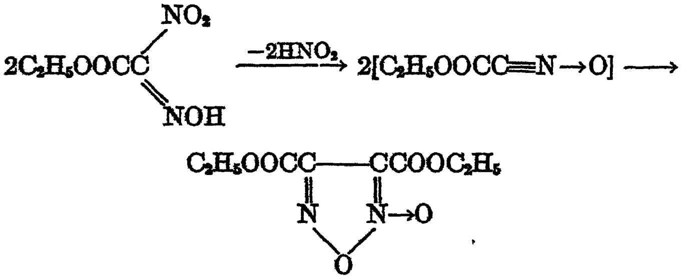


$$\underset{\text{NOH}}{\overset{\|}{\text{RC}}}\text{—X}$$

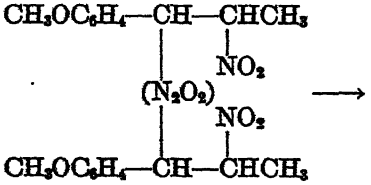
for by elimination of HX from these, the nitrile oxides often result. Thus the hydroxamic acid chlorides, with sodium bicarbonate, give furoxans (369, 363, 365).



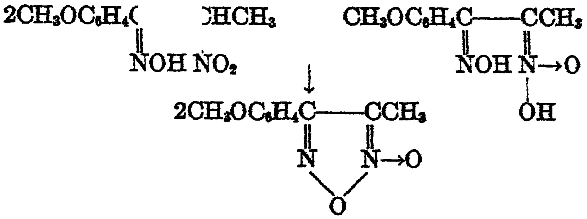
(*b*) By self-decomposition of many nitrolic acids (173, 172, 174).



(*c*) Disubstituted furoxans, R aromatic and R′ aliphatic, are obtained by boiling with water or alcohol the "pseudonitrosites" obtained from compounds of the type ArCH═CHCH$_2$Al (370, 4, 6, 373).



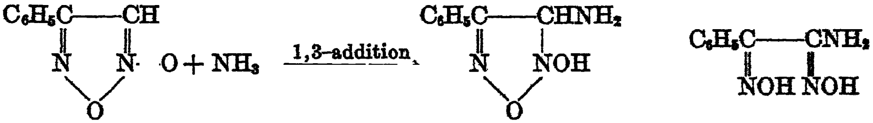
Anethole pseudonitrosite



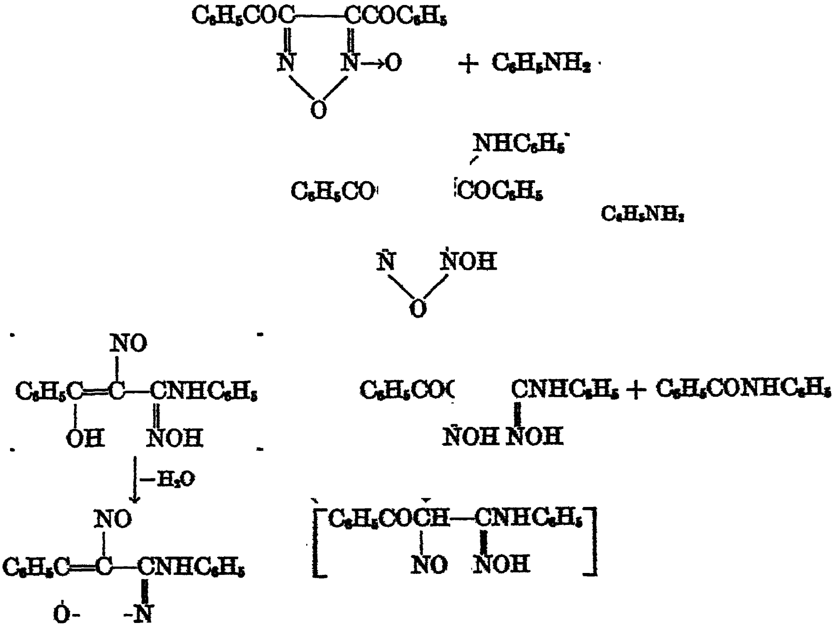
Hence the furoxans often result instead of the nitrosites when an ethylenic compound is treated with N_2O_3.

2. Behavior of the furoxans

The chief reaction is that with phosphorus pentachloride, giving furazan, phosphorus oxychloride, and chlorine. Hydriodic acid reduces furoxans to furazans, as do tin and hydrochloric acid. Monosubstituted furoxans are sensitive to alkali, but the disubstituted ones are stable; both types are stable to acids. With ammonia, the monosubstituted furoxans give amide oximes:



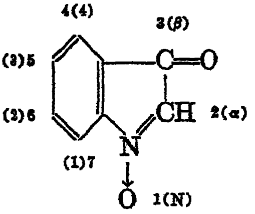
A reaction of the same type also occurs when disubstituted furoxans react with amines, providing one of the substituents is easily eliminated:

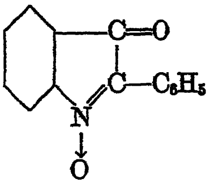


Nitroso isoxazole derivative

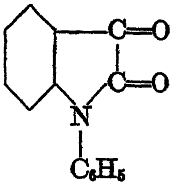
VI. THE ISATOGENS

The isatogens are derivatives of the ring system I, but the parent substance itself is unknown. Isatogens are isomeric with, and closely related to, the isatins. The ring system is numbered as shown (Ruggli) with Pfeiffer's system of numbering in parentheses. The first isatogens (IV and V) were discovered by Baeyer (317) during his work on the structure of indigo.

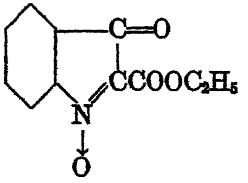




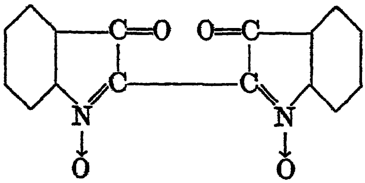
II
2-Phenylisatogen



III
N-phenylisatin



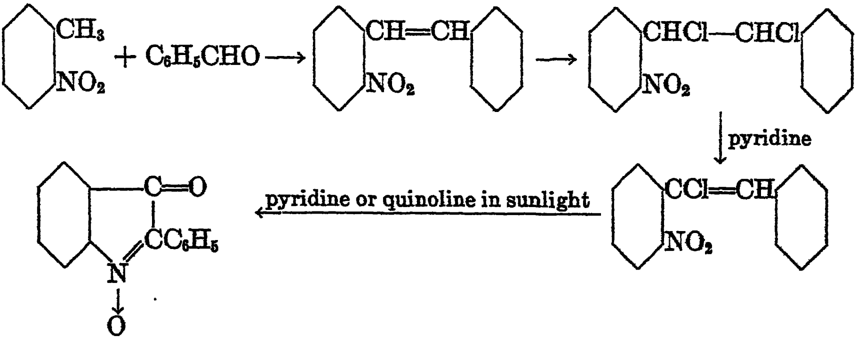
IV
Isatogenic ester



V
Diisatogen

Pfeiffer (284, 283) in 1916 discovered that isatogens could readily be made from *o*-nitrostilbene derivatives and from *o*-nitrotolanes by a rearrangement which takes place in pyridine in the presence of light. The isatogens are very interesting; not only do they contain the nitrone system, but this is conjugated with a carbonyl group. They show many properties characteristic of quinones; Pfeiffer has remarked that they were the "first meta-quinoid substances to be known with certainty."

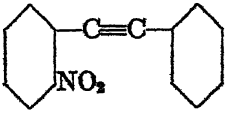
The starting materials for preparation of isatogens are *o*-nitrostilbenes, which are prepared by condensing *o*-nitrotoluene (and other *o*-nitromethyl hydrocarbons of the aromatic series) with aldehydes. When these stilbenes are chlorinated they give dichlorides; these, on warming with pyridine or quinoline, lose one mole of hydrochloric acid to give chlorostilbenes. If the colorless to bright yellow pyridine or quinoline solution of the chlorostilbene is placed in the sunlight, the color turns gradually to orange, then red, and orange to violet crystals appear; the yield is about 60 per cent and the product is easily purified by recrystallization.



Pfeiffer has made sixteen isatogens in this way and Ruggli has made several more. The most common one is 2-phenyl-6-nitroisatogen, which is made from 2,4-dinitrotoluene. Among the isatogen derivatives are nitriles, acids, esters, phenols, and nitro and methoxyl derivatives.

In a recent paper Ruggli (310) has described a new method of converting *o*-nitrotolane into 2-phenylisatogen. This consists in the action of nitrosobenzene upon the chloroform solution of *o*-nitrotolane in the dark. After standing for 19 days, the isatogen was produced in 57 per cent yield and in a very pure condition. The action of nitrosobenzene is apparently catalytic, for although the best yield of isatogen was obtained using 2 moles of nitrosobenzene per mole of *o*-nitrotolane, the amount of nitrosobenzene could be reduced to 0.2 mole without greatly affecting the results. Because the isatogen was obtained from *o*-nitrotolane more slowly than from the corresponding stilbene dichloride, Ruggli is inclined to the belief that radicals of the methylene type may be involved as intermediates in the formation of isatogens, and that the acetylenes (tolanes) require more time for conversion to these radicals than do the stilbene chlorides. The action of nitrosobenzene upon the tolanes is also supposed to involve intermediate radicals of the methylene type.

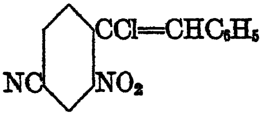
The isatogens contain no halogen and are isomeric with the *o*-nitrotolanes (A), but they are not tolanes, for the color of the isatogens is too deep and the real isatogens have entirely different physical and chemical properties.



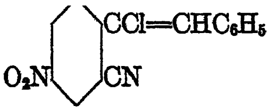
A

To obtain the isatogen from the monohalostilbene, both pyridine (or quinoline) and light are necessary; pyridine alone does not remove hydrochloric acid from the monochlorostilbenes. The tolanes can be obtained from the chlorostilbenes with hot, alcoholic potassium hydroxide; these, in pyridine and in the light, give the isatogens very easily. Pyridine cannot be replaced by benzene, alcohols, or acetic acid; solutions of the tolanes in any of these solvents are unchanged by the action of sunlight.

The mechanism of the isatogen formation is obscure; it may involve the tolanes, or it may not. Three processes seem to be involved, however: (*1*) hydrochloric acid is eliminated; (*2*) the oxygen migrates to the carbon next to the nitrated phenyl group; and (*3*) the ring closes. The ring closure follows from the fact that only *o*-nitrostilbenes give isatogens; thus compound VI gives an isatogen while compound VII does not.

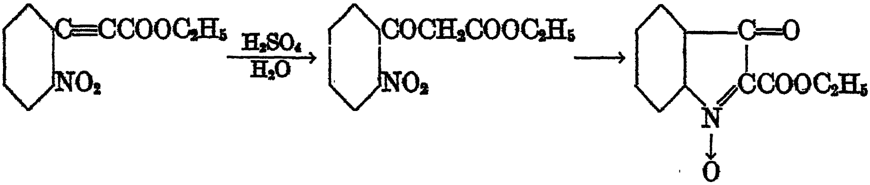


VI

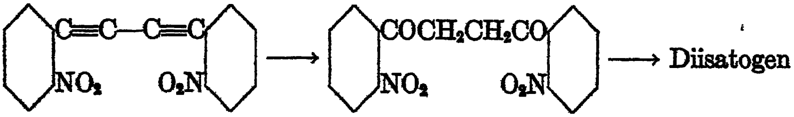


VII

The rôle of the pyridine seems to be that of a specific catalyst, for other solvents (except quinoline) are without effect. Isatogens can be made from the tolanes either photochemically in pyridine or sometimes, but not always, by the action of sulfuric acid. In the latter case the reaction consists first in the addition of water to the triple bond to give a ketone; this then condenses with the nitro group to give the isatogen.

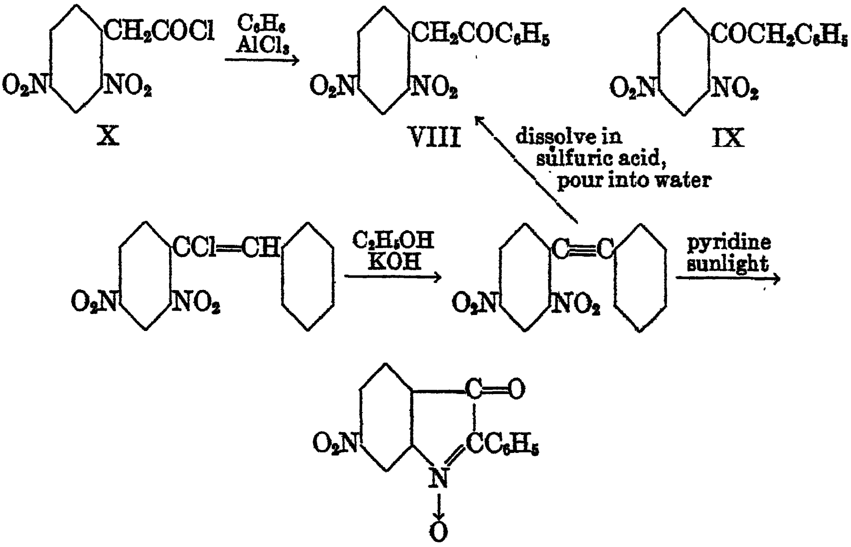


IV



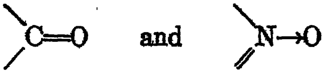
V

This mechanism also explains why sulfuric acid does not convert all *o*-nitrotolanes into isatogens; the water must add so that the resulting carbonyl group is next to the nitrated ring. Thus 2,4-dinitrotolane with sulfuric acid gives no isatogen; if the sulfuric acid solution is poured into water, the ketone (VIII) precipitates and this cannot form an isatogen, although its isomer (IX) could do so. That compound VIII was actually formed was proved by isolating it and by synthesizing it from 2,4-dinitrophenylacetyl chloride (X).

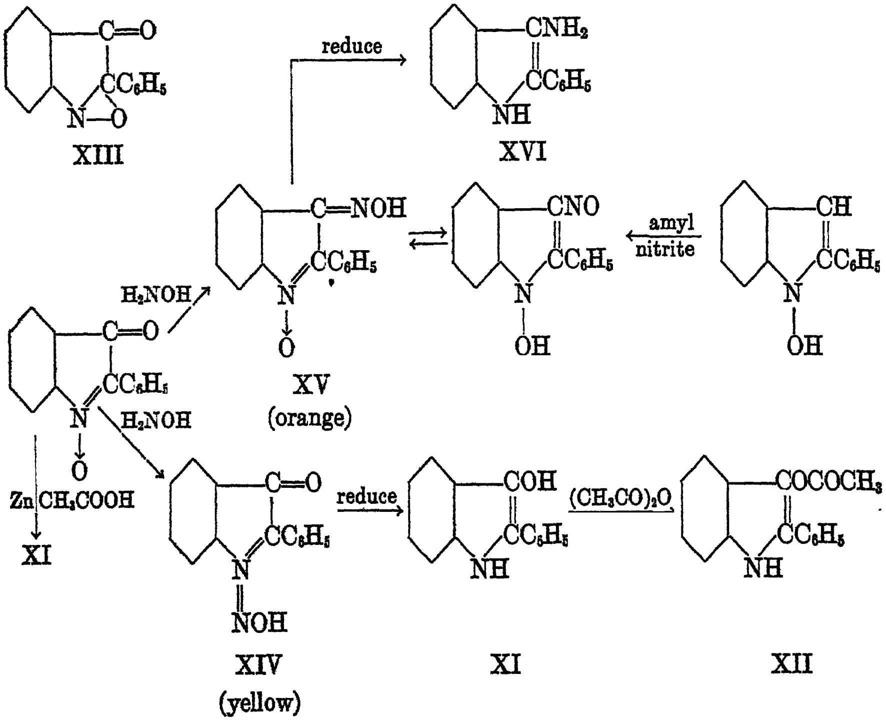


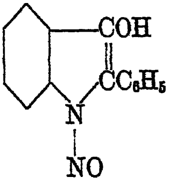
A. Structure of the isatogens

The isatogens are cyclic, for on reduction with zinc and acetic acid they give the almost colorless phenylindoxyls (XI); these, with acetic anhydride, give *O*-acetyl derivatives (XII). The formula shows two reactive groups:



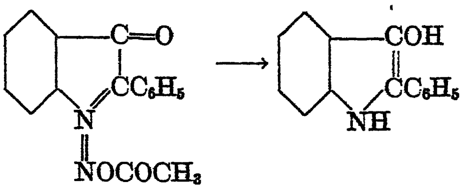
while the alternative structure (XIII) shows only one. The action of hydroxylamine hydrochloride in boiling alcohol (free hydroxylamine acts only as a reducing agent) gives *two isomeric oximes*, one of which (XIV) is yellow and is soluble in ammonia, giving a greenish solution; the other (XV) is orange and its solution in ammonia is also orange. With acetic anhydride these oximes give characteristic acetyl derivatives. The orange oxime is identical with a compound made by Angeli and Angelico (14) by the action of amyl nitrite on *N*-oxyphenylindole; this must therefore be the *C*-oxime:



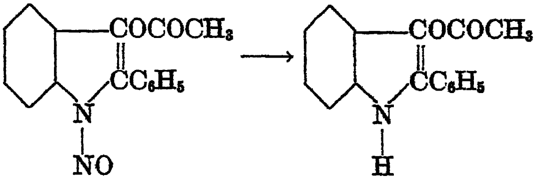


XVII

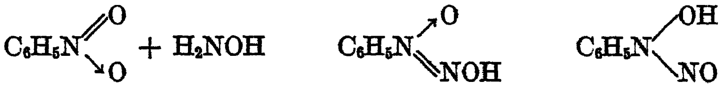
The yellow oxime is a *structural* isomer of the orange oxime. The orange oxime, on reduction, gives aminophenylindole (XVI). If the yellow oxime were a stereoisomer it should give the same reduction product, but it does not; instead, it gives phenylindoxyl (XI). Hence the yellow oxime must be the *N*-oxime or else the nitroso compound (XVII). The *N*-oxime formula is indicated by the fact that the acetylated yellow oxime on reduction (zinc and acetic acid) gives phenylindoxyl and no trace of acetylphenylindoxyl.



and not

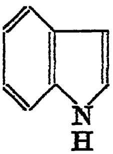


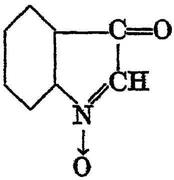
Hence the $>N\rightarrow O$ group can be converted to an oxime and so is like a carbonyl group. This may also be true of the nitro compounds, for nitrobenzene can be converted to nitrosophenylhydroxylamine by the action of hydroxylamine (13).



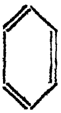
$$C_6H_5N\begin{smallmatrix}\nearrow O\\ \searrow O\end{smallmatrix} + H_2NOH \qquad C_6H_5N\begin{smallmatrix}\nearrow O\\ \searrow NOH\end{smallmatrix} \qquad C_6H_5N\begin{smallmatrix}\diagup OH\\ \diagdown NO\end{smallmatrix}$$

Comparing the formulas of indole (A) and isatogen (B), the relationship is seen to be the same as that between benzene (C) and quinone (D). Hence the isatogens should show quinoid character, and they do so. They are deeply colored, form quinhydrones (their hydroquinones are the indoxyls), and they liberate iodine from hydriodic acid.

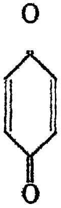




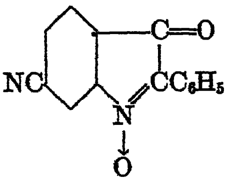
B



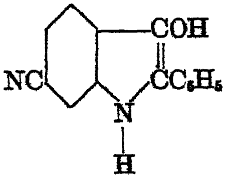
C



D



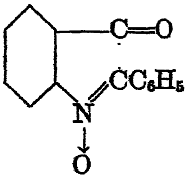
(orange)

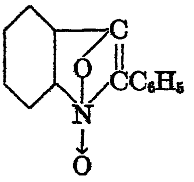


(colorless)

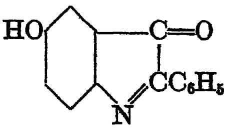
The mixture of the orange cyanoisatogen and the colorless cyanoindoxyl gives a black, crystalline compound easily separated into its components again. Hence these substances are really "quinoids," in which the >N→O group plays the part of one carbonyl group. Baeyer's isatogenic ester and diisatogen are really isatogens of the same type as these, and they do not have the three-membered ring as Baeyer wrote them.

But the matter is somewhat more complicated than just outlined. If 2-phenylisatogen is treated with alcoholic hydrochloric acid, there results a yellow isomer which is stable to light and sulfuric acid. The yellow isomer forms an oxime (only one) which is different from either of the oximes of the original isatogen. Hence it must contain a carbonyl group; but it shows no quinoid properties and does not liberate iodine from a solution of potassium iodide in acetone. Both isomers have the same composition *and* molecular weight; the isoisatogen is not compound XIX, for it shows no phenolic properties (gives no color with ferric chloride, is not stable in alkali, is stable to bromine at ordinary temperatures, does not couple with diazonium compounds, etc.). A structure such as that shown in formula XVIII is excluded on stereochemical grounds and also because of the lack of oxidizing power. Both isomers on reduction give the same indoxyl. Heated for 5 min. above its melting point or in glacial acetic acid solution, or, most smoothly of all, when it is heated with phenyl isocyanate, the isoisatogen reverts to the normal isatogen. The only possible structure for this isoisatogen, on the basis of the evidence so far, is one that contains the three-membered ring (XX).

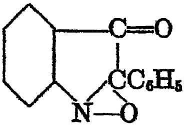




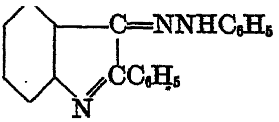
XVIII



XIX



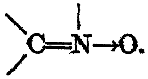
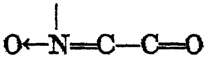
XX



XXI

The normal isatogens and the isoisatogens behave differently toward phenylhydrazine; the normal isatogen is reduced to indoxyl (like the action of phenylhydrazine on quinone to give hydroquinone), while the isoisatogen gives a compound analyzing for formula XXI or else it does not react at all. It is not possible to be sure, as yet, of any of the structures in the iso series.

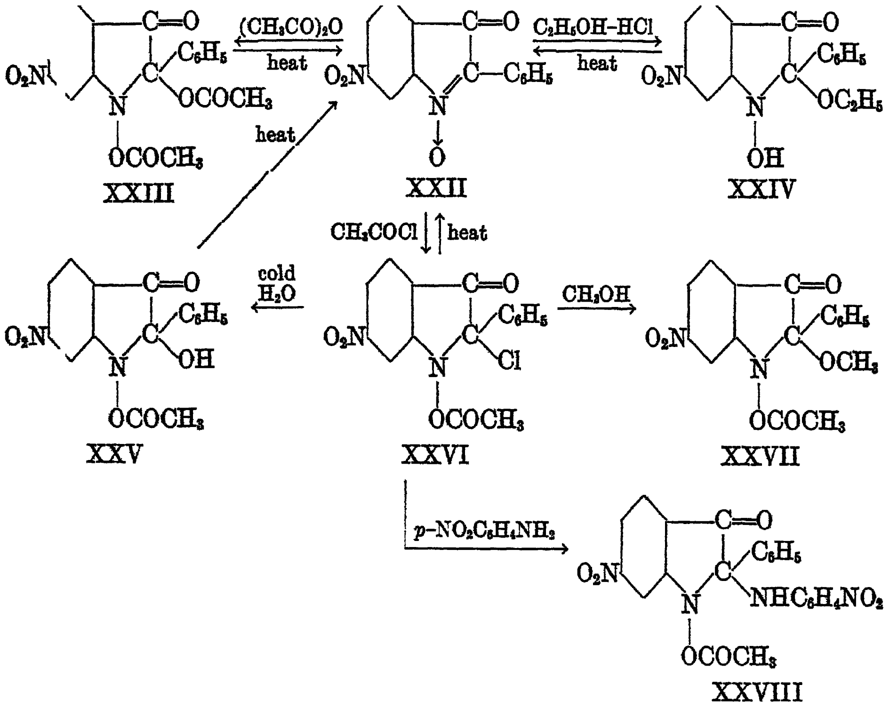
B. Chemical properties of the isatogens (309, 312, 313)

The isatogens add a wide variety of reagents including acetyl chloride, acetic anhydride, and alcohols; some of these reactions are certainly 1,3-additions and probably most of the other reactions involve initial 1,3-additions also. When the *deep red* 6-nitro-2-phenylisatogen (XXII) is refluxed with acetyl chloride for a few hours, a yellow solution results (309). If the solvent is evaporated in the absence of all traces of water, large yellow crystals of the addition compound (XXVI) result. This addition product decomposes into the components when heated to 145–160°C., but it is stable at room temperature for some time, though not indefinitely, providing care is taken to keep it dry. It is very reactive when in solution and often the yellow solution turns red, owing to the formation of the isatogen by the action of traces of water upon XXVI. The chloro compound is even more sensitive when attempts are made to replace the chlorine by other groups. Aniline and phenylhydrazine react instantly, giving the isatogen (XXII), which then reacts further when phenylhydrazine is used. But with an amine less basic than aniline, such as *p*-nitroaniline, the chlorine atom is replaced and the product is compound XXVIII. The product (XXVI) must have the structure shown and must be formed by 1,3-addition to the nitrone system  $\rangle C{=}\overset{|}{N}{\rightarrow}O$. The nitro group in the benzene ring cannot be involved, for the corresponding isatogen without the nitro group gives the same reaction with acetyl chloride, and while a reaction with the system  $O{\leftarrow}N{=}\overset{|}{C}{-}C{=}O$ was considered, this possibility was rejected because it would involve the attachment of the chlorine atom to oxygen. The structure XXVI shows no "quinoid" linkage, which agrees with the properties in so far as the substance is stable enough to investigate; compound XXVI is lighter in color than the isatogen and is not derived from the isoisatogen, for the latter does not react with acetyl chloride. Substance XXVIII also dissociates when heated, giving the isatogen (XXII), acetic acid, the amine, and a small amount of the isoisatogen. Tests for the carbonyl group in compound XXVIII were negative; hydroxylamine, phenylhydrazine, and semicarbazide under varied conditions gave only orange colors and the dissociation products of XXVIII. Methanol and ethanol react with XXVI in the same manner as nitroaniline; the products are the ethers (XXVII). The reaction with alcohols often gives rise to the isatogen, but once the ether is formed, it is quite stable. These ether-acetates cannot be made by the direct addition of alkyl acetates to the nitrone.

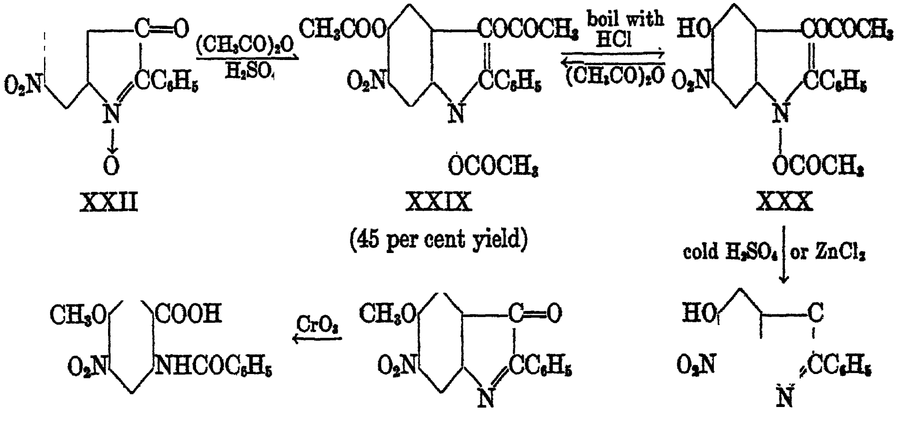
When the solution of XXVI in acetyl chloride is poured into water, a yellow precipitate results which is quickly transformed into the isatogen by the heat evolved. If, however, the solution is poured onto ice, the yellow precipitate remains and on careful purification the substance XXV is obtained. This dissociates at 125°C. into acetic acid and the isatogen, but the substance cannot be made directly from its components.

Other acid halides (C_6H_5COCl, $SOCl_2$, SO_2Cl_2, BrCN) either did not react with XXII or else led to resins, but acetic anhydride in great excess produced the addition product XXIII, although the reaction was never complete. No carbonyl group could be detected in compound XXIII.

The action of cold alcoholic hydrochloric acid upon the isatogen (XXII) produced the addition product (XXIV), and it was considered likely that hydrochloric acid added first, followed by replacement of the chlorine by the ethoxyl group. The addition product (XXIV) is very labile and is quite different from the isoisatogen produced from XXII by the action of hot, alcoholic hydrochloric acid.



The isatogen behaves like quinone toward acetic anhydride in the presence of sulfuric acid (312), giving a triacetate with one of the acetoxy groups in the benzene ring. The product (XXIX) was degraded to the ketoindolenine (XXXI) and then to the acid (XXXIII), both of which were synthesized by independent methods. In the formation of XXIX, there is obtained a red, crystalline by-product, isomeric with the isatogen. This is the *N*-phenylisatin (XXXIV), formed by Beckmann rearrangement of the isatogen (the isatogen is in effect the *N*-ether of an oxime). This isatin gives a phenylhydrazone, an oxime, etc., and with *o*-phenylenediamine gives a phenazine (XXXV).



XXII

XXIX

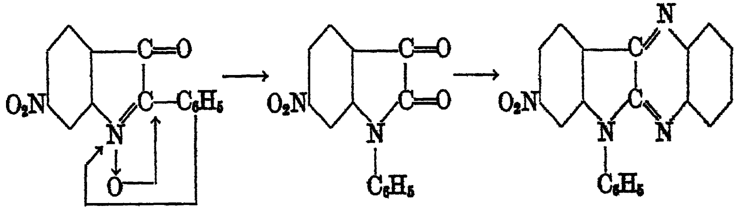
(45 per cent yield)

XXX

XXXIII

XXXII

XXXI



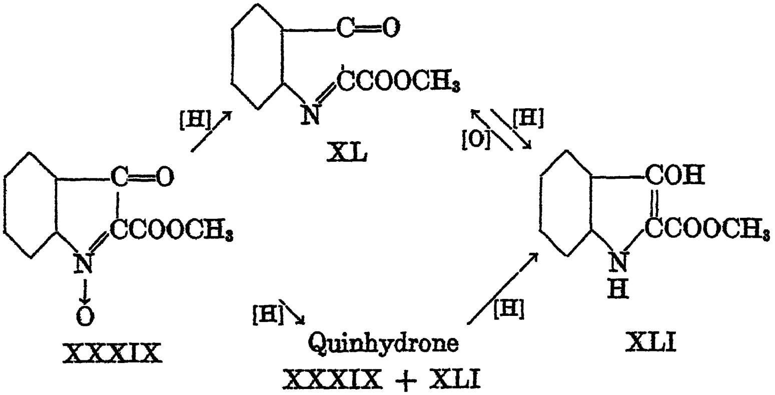
XXII

XXXIV

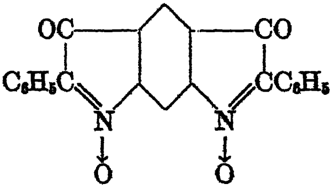
XXXV

Reduction of isatogens (314) is difficult to interrupt short of the final product, which is an indoxyl. But by using the methyl ester of isatogenic acid (XXXIX) it was possible to show that the reduction occurred stepwise as follows:

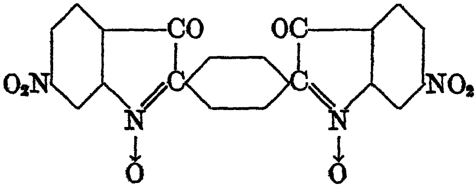
$$\begin{tikzcd}
& \text{ketoindolenine} \arrow[dr, shift left] & \\
\text{isatogen} \arrow[ur] \arrow[dr] & & \text{indoxyl} \arrow[ul, shift left] \\
& \text{"quinhydrone"} \\ \text{(isatogen + indoxyl)} \arrow[ur] &
\end{tikzcd}$$



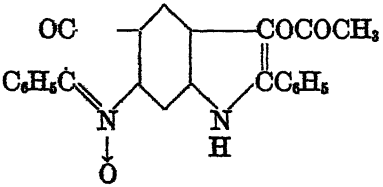
Ruggli and Disler (311) have prepared isatogens derived from anthraquinone, using the general method starting with anthraquinone-2-aldehyde and 2,4-dinitrotoluene. Ruggli, Zimmermann, and Thouvay (316) sought to prepare the diisatogen (XXXVI) starting with 4,6-dinitro-1,3-xylene, but the ring closure could be made to take place only on one side. However, the isatogen-indoxyl derivative (XXXVII) was prepared (315).



XXXVI



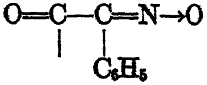
XXXVIII



XXXVII

Recently (317) diisatogens have been made in which the two isatogen rings are separated by a benzene ring, starting with *m*- and *p*-phthalaldehydes and 2,4-dinitrotoluene. The reactions used were the usual ones. The product from *p*-phthalaldehyde was XXXVIII. *o*-Phthalaldehyde would condense only once with 2,4-dinitrotoluene, hence no diisatogen was obtained in this case.

Thus the isatogens are nitrones with the system $>C{=}\overset{|}{N}\rightarrow O$ and most of their reactions which have been studied in detail can logically be interpreted as 1,3-additions. The isatogens are also "quinoid," for the nitrone system is conjugated with a carbonyl group to give the system

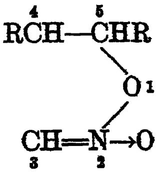


$$O{=}\underset{|}{C}{-}\underset{\underset{\displaystyle C_6H_5}{|}}{C}{=}N\rightarrow O$$

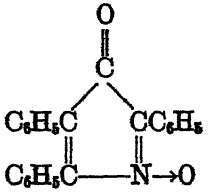
and the isatogens therefore could give reactions starting at the carbonyl or nitrone group and ending at the other system. These would be 1,5-additions; the further study of the chemical properties of these curious compounds cannot but produce results of great interest and theoretical importance.

VII. THE ISOXAZOLINE OXIDES AND DERIVATIVES

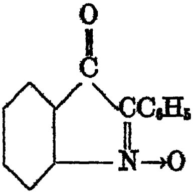
The isoxazoline oxides contain a five-membered ring system (I) in which the nitrone system is a part of the ring. The cyclic nitrones (II), which are closely related to and derived from the isoxazoline oxides, also contain the nitrone system as part of a ring. However, in the isoxazoline oxides this system stands alone, while in the cyclic nitrones the nitrone system is conjugated with a carbonyl group as it is in the isatogens (III):



I



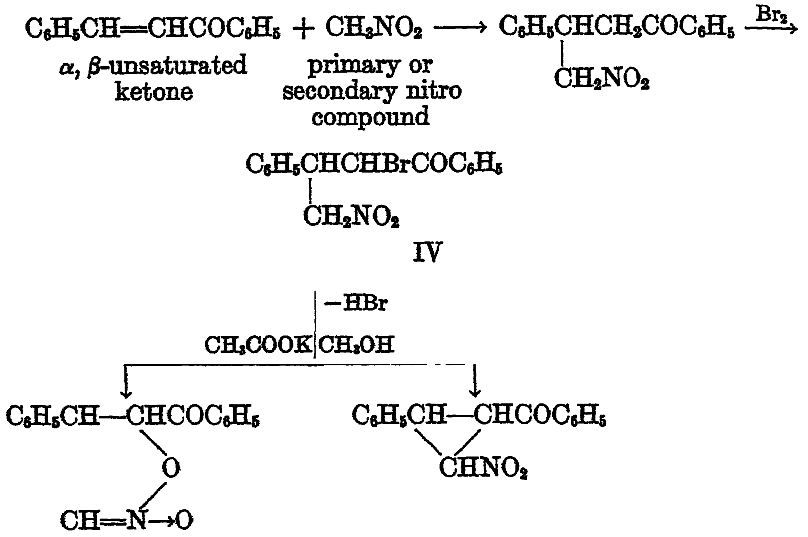
II



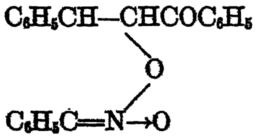
III

Thus the cyclic nitrones are really mononuclear isatogens and like the isatogens they are "quinoids,"—deeply colored (dark purple). The nitrone system in both of these compounds is extremely reactive, undergoing 1,3-additions; they are very sensitive, combining even with the solvent unless special precautions are taken. The work upon these two classes of compounds was done by Kohler and his students and is reported in a series of papers (179–195) which appeared during the period 1924–1930.

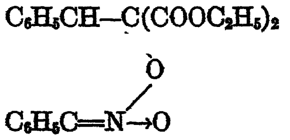
The isoxazoline oxides were first discovered as by-products in the preparation of the nitrocyclopropanes, for which the usual synthesis includes the following steps:


C₆H₅CH=CHCOC₆H₅ + CH₃NO₂ → C₆H₅CHCH₂COC₆H₅ (CH₂NO₂) →Br₂
α, β-unsaturated ketone
primary or secondary nitro compound
C₆H₅CHCHBrCOC₆H₅ (CH₂NO₂)
IV
−HBr
CH₃COOK | CH₃OH
C₆H₅CH—CHCOC₆H₅, O, CH=N→O
C₆H₅CH—CHCOC₆H₅, CHNO₂

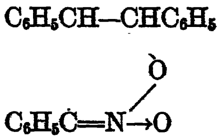
The stereoisomeric α-bromo-γ-nitroketones (IV) behave quite differently when hydrobromic acid is eliminated from them by means of potassium acetate in methanol; some of them give only cyclopropanes, certain representatives give mixtures of cyclopropanes and isoxazoline oxides, while others give the oxide alone. The synthesis outlined can be varied somewhat, but the product is always an isoxazoline oxide with a group COR (R = alkyl, aryl, or *O*-alkyl) in the 5-position. Thus if phenylnitromethane is used instead of nitromethane, the oxide will be V; if benzalmalonic ester and phenylnitromethane, or nitrostilbene and malonic ester, are used, the oxide will be VI. Similarly, if nitrostilbene and phenylnitromethane are used, the oxide will be VII, but in the last case the elements of nitrous acid, instead of hydrobromic acid, are eliminated in the final step. Isoxazoline oxides prepared from these starting materials do not have the group COR in the 5-position.



V

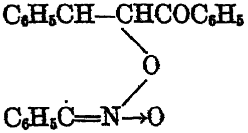


VI

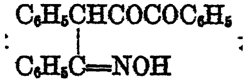


VII

To obtain the cyclic nitrones the only method available consists in starting with the isoxazoline oxide (V) obtained from α,β-unsaturated ketones and substituted nitromethanes such as phenylnitromethane. Isoxazoline oxides of the type of V, on standing in ether or alcoholic solution, spontaneously isomerize into a yellow triketone oxime (VIII), and the latter then isomerizes to 5-hydroxy-5-benzoylisoxazoline (IX). All three of these compounds V, VIII, and IX exist in equilibrium with each other, and if the yellow triketone oxime (VIII), or any of the substances in equilibrium with it, is dissolved in chloroform and a trace of acid is added, the deep purple nitrone results, probably *via* the intermediates XI and XII:

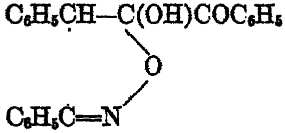


V
(colorless)

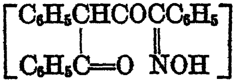


$$\begin{array}{l} C_6H_5CHCOCOC_6H_5 \\ C_6H_5C{=}NOH \end{array}$$

VIII
(yellow)

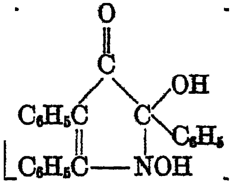


IX
(colorless)



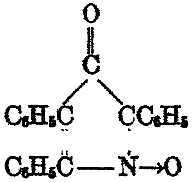
$$\left[\begin{array}{l} C_6H_5CHCOCC_6H_5 \\ C_6H_5C{=}O\quad NOH \end{array}\right]$$

XI



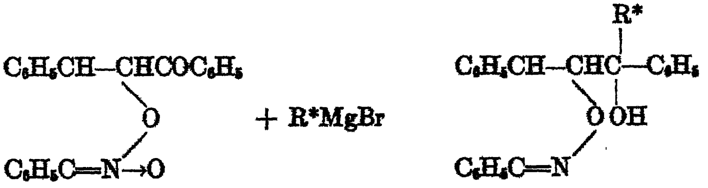
XII

$-H_2O$



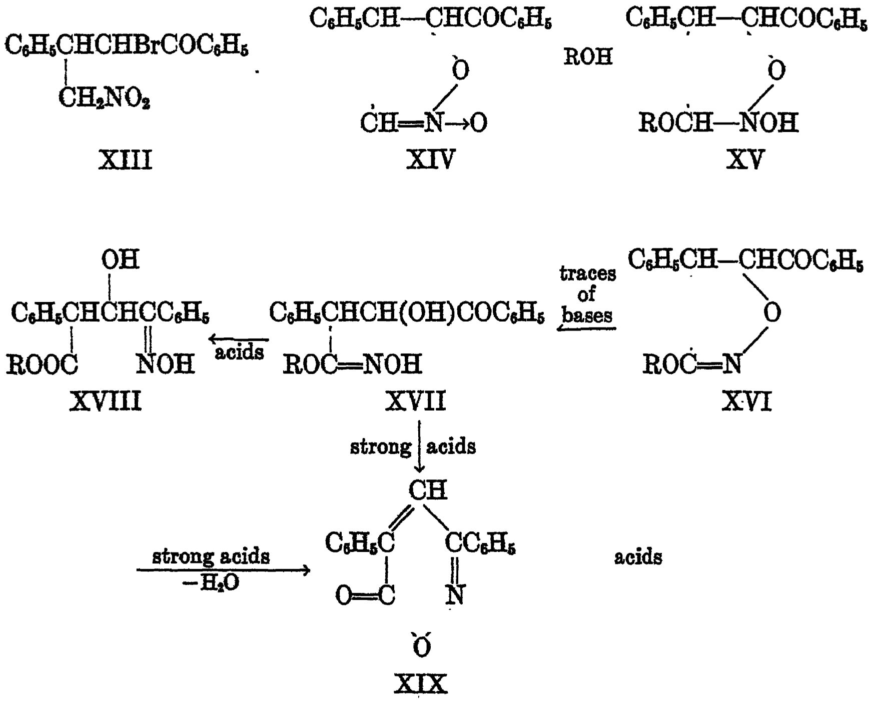
X
(deep purple)

The reactions of these compounds are extremely complicated, chiefly because most of the ones studied were of the type of compound V, which contains the carbonyl group in the 5-position. This is not conjugated with the nitrone system, but it can react with many reagents that would be used in a study of the nitrone system; moreover, it mobilizes the hydrogen in the $\alpha(5)$-position, causing easy loss of water and giving rise to a whole series of rearrangements which are very difficult to follow. Thus with the Grignard reagent there could be either 1,3-addition to the nitrone system, 1,2-addition at the carbonyl group, or reduction, and in the case of the ketonic oxides, the last two of these reactions predominate. Thus:



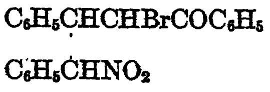
(*R = C_2H_5 or C_6H_5)

Moreover, oxides of the type of V are extremely sensitive toward acids and bases and they can be isolated only in favorable cases. In general, the rearrangements involved (all of which start as rearrangements of the isoxazoline oxide) in the case of the ketonic oxides may be summed up as follows: primary nitroketones, such as XIII, first give the corresponding isoxazoline oxides (XIV); these cannot be isolated, for they at once add a molecule of the solvent (ROH) 1,3 to the nitrone system giving the intermediate (XV), which then loses water and rearranges to the isoxazole (XVI).

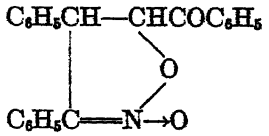


The latter may undergo further rearrangements; acids convert the isoxazole directly to the ortho-oxazine (XIX), while mild bases convert the isoxazole to the hydroxamic ester (XVII). The latter, in turn, is converted to the oximino ester (XVIII) by weak acids, but the action of strong acids upon either XVII or XVIII produces the ortho-oxazine (XIX).

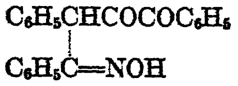
Secondary nitroketones such as XX first give the corresponding isoxazoline oxides (XXI), which in basic media give either monoöximes of triketones (XXII) or ketonic isoxazoles (XXIII); in *acid* media they give hydroxyisoxazolines (XXIV) or ortho-oxazines (XXV)



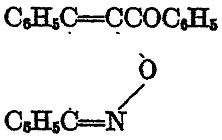
XX



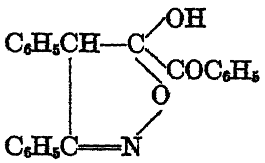
XXI



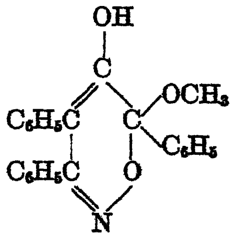
XXII



XXIII

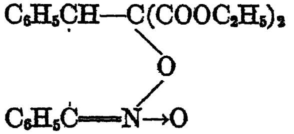


XXIV

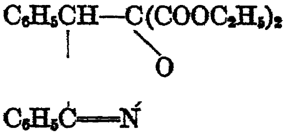


XXV

Aside from these complications due to rearrangements, the isoxazoline oxides show the reactions of 1,3-systems. They liberate chlorine from phosphorus pentachloride and are thus converted to isoxazoles, from which the oxides may be regenerated by the action of hydrogen peroxide.

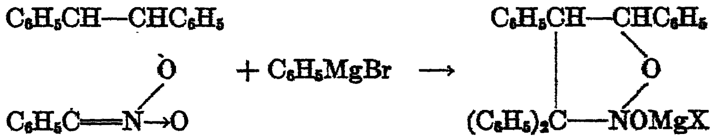


XXVI

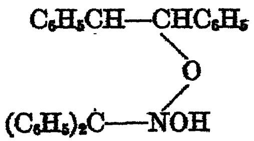


XXVII

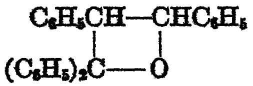
The oxides react with the Grignard reagent, giving a primary 1,3-addition. The reaction is very complicated when ketonic oxides, with the —COR group in the 5-position, are used. In the case of triphenylisoxazoline oxide (XXVIII) it was possible to follow the course of the Grignard reaction, although all Grignard reagents do not react alike. With phenylmagnesium bromide the reaction involved the following steps:



XXVIII XXIX

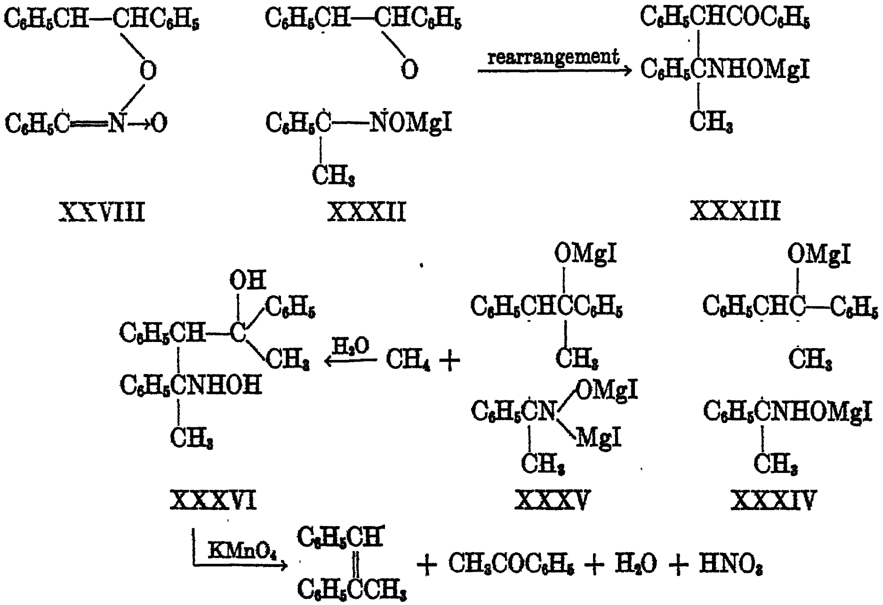


XXX



XXXI

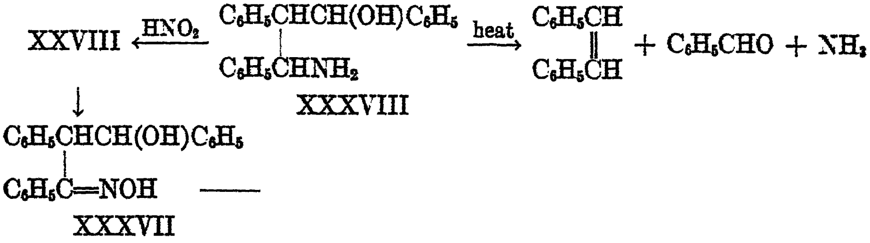
With methylmagnesium iodide the reaction was not confined to 1 mole of the Grignard reagent; instead, the oxide (XXVIII) consumed 3 moles of the reagent and liberated 1 mole of methane. The product was a basic substance containing two active hydrogen atoms (analysis in the "machine") and having the composition $C_{23}H_{25}O_2N$. This base could be acetylated to give mono- or di-acetates, and on oxidation of the base by permanganate the products were water, nitric acid, acetophenone, and methylstilbene. The structure of the base was therefore that of XXXVI, and the reaction of the oxide (XXVIII) with methylmagnesium iodide involved the following steps, the first of which was 1,3-addition of the reagent to the nitrone linkage:


XXVIII XXXII XXXIII

XXXVI XXXV XXXIV

The reaction between the oxide (XXVIII) and ethylmagnesium bromide was still more complicated; 2.8 moles of the reagent was consumed and 0.6 mole of gas was liberated. The gas consisted of ethane and ethylene (4:1) and the addition reaction was complicated by the reducing action of the ethylmagnesium bromide. No addition product could be isolated, but the reduction product, identical with that produced from the oxide by zinc and acetic acid, was isolated.

Reduction of triphenylisoxazoline oxide (XXVIII) produces the β-hydroxy oxime (XXXVII), which can be reduced further to the amine (XXXVIII). When heated, the amine decomposes into stilbene, benzaldehyde, and ammonia, but when subjected to the action of nitrous acid the amine does not give the expected dihydroxy compound; instead, the isoxazoline oxide results.



$$\mathrm{XXVIII} \xleftarrow{HNO_2} \begin{array}{l} C_6H_5CHCH(OH)C_6H_5 \\ \quad | \\ C_6H_5CHNH_2 \end{array} \xrightarrow{heat} \begin{array}{l} C_6H_5CH \\ \quad \| \\ C_6H_5CH \end{array} + C_6H_5CHO + NH_3$$

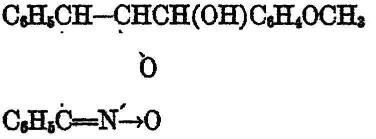
XXXVIII

$$\downarrow$$

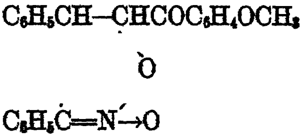
$$\begin{array}{l} C_6H_5CHCH(OH)C_6H_5 \\ \quad | \\ C_6H_5C{=}NOH \quad — \end{array}$$

XXXVII

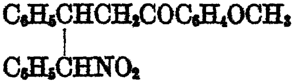
Reduction of the ketoisoxazoline oxides introduces additional complications because the three reducible groups—carbonyl, nitrone, and oxido ring—compete for the hydrogen. By hydrogenating the keto oxide (XXXIX) in the presence of platinum oxide catalyst and stopping the reaction when 1 mole of hydrogen had been absorbed, two products were isolated: the hydroxy oxide (XL), formed by reduction of the carbonyl group, and the nitro compound (XLI) formed either by primary reduction of the nitrone linkage followed by rearrangement, or by reduction of the oxido ring to the *aci*-nitro compound. The hydroxyisoxazoline oxide (XL), when reduced further, is transformed into an amine analogous to the one obtained by reduction of XXVIII.



XL
(75 per cent)



XXXIX

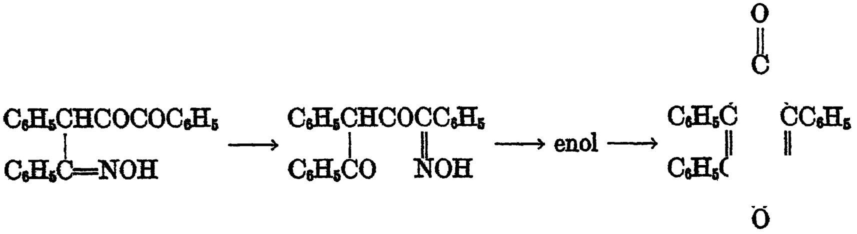


$$\begin{array}{l} C_6H_5CHCH_2COC_6H_4OCH_3 \\ \quad | \\ C_6H_5CHNO_2 \end{array}$$

XLI

A. The cyclic nitrones (184, 53, 52, 54)

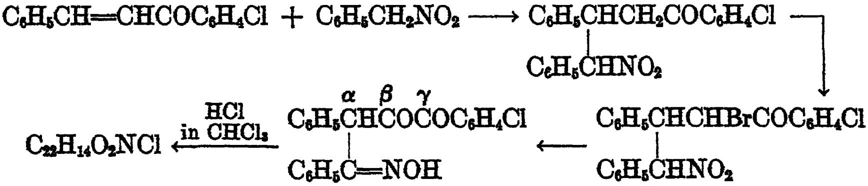
As mentioned before, when solutions of triphenylbutanetrione oxime (VIII) become acid, there appears in small quantities a purple anhydride (X) which is a monomolecular anhydride of the oxime. No open-chain anhydride can be derived from an oxime of the structure of VIII, and the only anhydride of the enol of VIII is the isoxazole (IX). Hence the formation of the purple anhydride must be preceded by rearrangement, but since the slightest trace of acid is sufficient to cause this, it is not likely that the carbon chain rearranges. However, transportation of the oximino group to a more active carbonyl group is not improbable and such a shift would be favored in acid media, thus leading to a new anhydride.



VIII XI XLII

$$\text{or XI} \longrightarrow \text{XII} \longrightarrow \text{X}$$

Attempts to determine by ozonolysis whether or not XLII was a possible structure failed because the products, benzoic acid and benzonitrile, are not sufficiently significant. Hence it was necessary to mark one of the phenyl groups and therefore an analog of VIII was synthesized as follows:



$$C_6H_5CH{=}CHCOC_6H_4Cl + C_6H_5CH_2NO_2 \longrightarrow \begin{array}{l} C_6H_5CHCH_2COC_6H_4Cl \\ \;| \\ C_6H_5CHNO_2 \end{array}$$

$$\underset{\text{XLIV}}{C_{22}H_{14}O_2NCl} \xleftarrow[\text{in } CHCl_3]{HCl} \underset{\text{XLIII}}{\begin{array}{l} \quad\;\;\alpha\;\;\beta\;\;\gamma \\ C_6H_5CHCOCOC_6H_4Cl \\ \;| \\ C_6H_5C{=}NOH \end{array}} \longleftarrow \begin{array}{l} C_6H_5CHCHBrCOC_6H_4Cl \\ \;| \\ C_6H_5CHNO_2 \end{array}$$

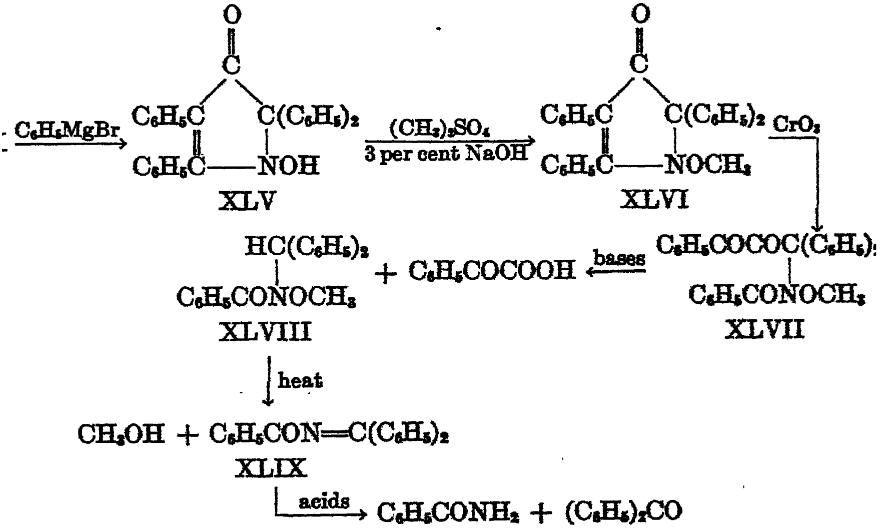
Ozonolysis of XLIV gave benzoic acid and chlorobenzonitrile; hence the nitrogen in the anhydride is attached to what was the γ-carbon atom of the oxime. This evidence reduces the plausible formulas for the anhydride to two: XLII and X. To distinguish between XLII and X the action of methylmagnesium iodide upon the anhydride was investigated quantitatively. The anhydride consumes 3 moles of the reagent, liberating 1 mole of gas. Since there is no apparent reason why the ortho-oxazine (XLII) should liberate gas, while the isoxazoline oxides always do, formula X for the anhydride becomes the more probable one. The physical properties of the product formed by the addition of methylmagnesium iodide to the anhydride rendered the compound unsuitable for investigation, and phenylmagnesium bromide gave a product (XLV) which was stable only in the solid form. In solution the product changes too rapidly for molecular weight determinations to be made and analysis alone does not give any information as to the quantity of phenylmagnesium bromide which reacts with the anhydride. Therefore *p*-bromophenylmagnesium bromide was used and in this case analysis of the product showed that the anhydride reacted with only 1 mole of Grignard reagent. Ozonolysis of XLV was inconclusive, but careful oxidation with chromic acid gave benzoic acid and a substance identified as $C_6H_5COCOC(C_6H_5)_2OH$. Though the formation of these products is not sufficient to establish the structure of the product, it is evident that the Grignard reagent does not react with the carbonyl group. Since the product obtained from the anhydride and the Grignard reagent was so unstable, it was converted to the stable methyl ether (XLVI) before degradation. The methyl ether has the composition $C_{29}H_{23}O_2N$, which is equal to that of the purple compound + C_6H_6 + CH_2. The ether is stable to acids and bases, and by careful oxidation with chromic acid it is possible to add two atoms of oxygen without disrupting the molecule. This oxidation product (XLVII) is readily attacked by bases, cleaving smoothly to benzoylformic acid and a nitrogen compound:

$$\underset{\text{XLVII}}{C_{29}H_{23}O_4N} + H_2O \longrightarrow C_6H_5COCOOH + \underset{\text{XLVIII}}{C_{21}H_{19}O_2N}$$

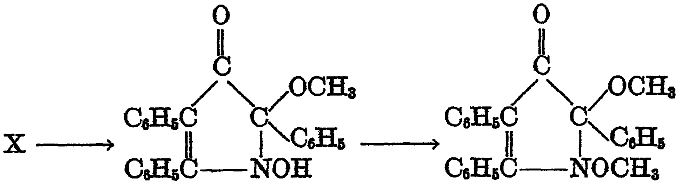
When this nitrogen compound (XLVIII) is heated above its melting point it loses the elements of methanol, giving another nitrogen compound (XLIX); the latter was hydrolyzed by acids to benzophenone and benzamide:

$$\underset{\text{XLVIII}}{C_{21}H_{19}O_2N} \longrightarrow CH_3OH + \underset{\text{XLIX}}{C_{20}H_{15}ON} \xrightarrow{H_2O} (C_6H_5)_2CO + C_6H_5CONH_2$$

The formation of these degradation products constitutes a very complete proof that the purple compound is the cyclic nitrone (X).

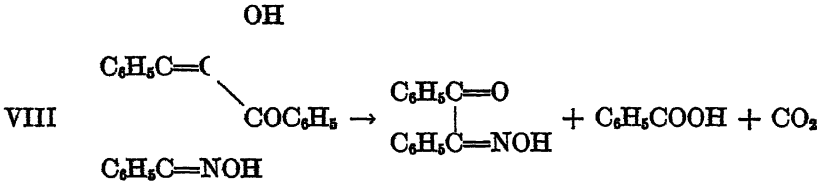


Thus the purple compound is a cyclic nitrone and it reacts with Grignard reagents by 1,3-addition. The nitrone, when heated with sodium methoxide and then acidified, adds a molecule of methanol. The product closely resembles in color and instability that obtained by adding the Grignard reagents, and, like the latter, it forms a very stable methyl ether. These products must therefore be L and LI, and the former is a result of 1,3-addition of methanol to the nitrone system.

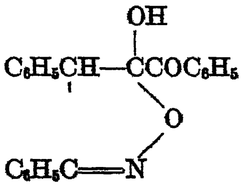


L LI

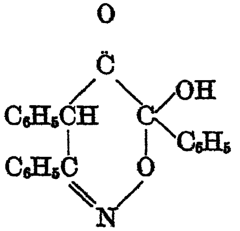
It is not possible to say much regarding the mechanism by which the purple compound is formed from the oxime; the open-chain formula for the oxime is based largely on its oxidation to α-benzil monoöxime by sodium peroxide:



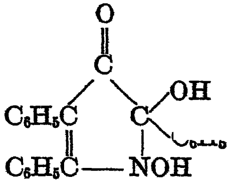
It is hard to reconcile these oxidation products with any other formula for VIII, but no open-chain derivatives of the oxime are known. All reagents that do not disrupt the molecule transform the oxime either to a cyclic isomer or to derivatives of cyclic isomers of the types A, B, or C.



A



B



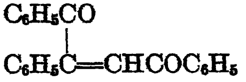
C

It may be that these forms A, B, and C are all present in the solutions of this very active substance; if so, X is merely the dehydration product of C.

The 1,3-addition reactions of the nitrones are, however, evidently subject to the same kind of hindrance as the 1,4-additions of the α,β-unsaturated ketones. For while the *N*-phenyl and *N*-benzyl ethers of diphenylacetaldoxime do not combine with Grignard reagents or alkoxides, these purple nitrones, though equally highly substituted, still combine readily with both.

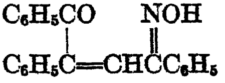
Recently Blatt (52, 53, 54), in a study of the action of hydroxylamine upon unsaturated 1,4-diketones, has discovered a very interesting case of ring-chain tautomerism involving a nitrone and an oxime. The action of hydroxylamine hydrochloride upon phenyldibenzoylethylene (LII) produces two isomeric compounds. One of these LV is bright yellow and is stable only in neutral and acid solutions; the other (LIII) is pale yellow, and is stable only in alkaline or pyridine solutions, although it can be obtained in an impure state by careful acidification of its solution in alkali. The isomers are interconvertible, but rapid conversion of LIII into LV is effected only by the halogen acids, and hence either LIII or LV can be obtained by acidification by proper acids of solutions containing the sodium derivative of LIII; the action of acetic acid produces LIII, while the action of hydrochloric acid produces LV.

The alkali-stable substance (LIII) is the monoöxime of LII, for it can be converted into benzoyl and acetyl derivatives from which it can be regenerated, and both the alkaline and pyridine solutions of LIII undergo the Beckmann rearrangement, giving LIV.



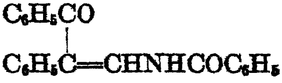
$\overset{C_6H_5CO}{\overset{|}{C_6H_5C}}=CHCOC_6H_5$

LII



$\overset{C_6H_5CO}{\overset{|}{C_6H_5C}}=CH\overset{NOH}{\overset{\|}{C}}C_6H_5$

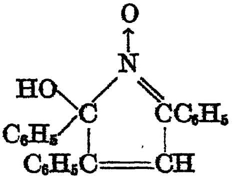
LIII



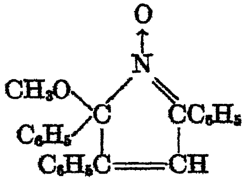
$\overset{C_6H_5CO}{\overset{|}{C_6H_5C}}=CHNHCOC_6H_5$

LIV

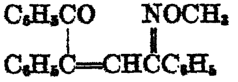
The acid-stable isomer is not a stereoisomer of LIII, but is the cyclic hydroxynitrone (LV). When LV is boiled with methanol and hydrochloric acid, the product is the methyl ether (LVI), and the latter on reduction with zinc and acetic acid gives the pyrrole (LVII). The reaction involves an initial 1,3-addition of hydrogen followed by a 1,4-elimination of methanol to give LVIII, which is then reduced to LVII.



LV



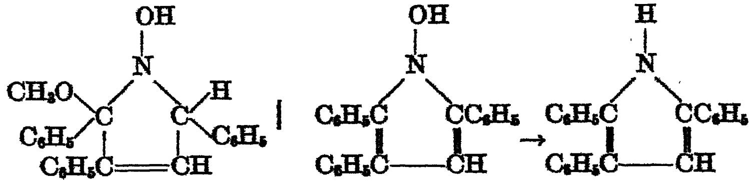
LVI



$\overset{C_6H_5CO}{\overset{|}{C_6H_5C}}=CH\overset{NOCH_3}{\overset{\|}{C}}C_6H_5$

LIX

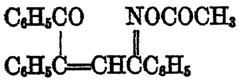
LVI ·



LVIII LVII

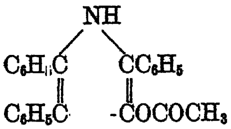
When LVI reacts with sodium–potassium alloy, or with Grignard reagents, the product is LVIII, which on further reduction with zinc and acetic acid gives the pyrrole (LVII).

Alkylation of LIII in alkaline solution produces largely derivatives of LV. The action of methyl iodide and sodium methoxide upon LIII gives the methyl ether (LVI); while the action of methyl sulfate and sodium hydroxide produces LVI and also LIX, the methyl ether of the oxime (LIII). Acetylation of LIII by acetyl chloride produces LX, which is stable toward acetic anhydride and which is the acetate of LIII.

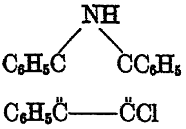


$$\begin{array}{ll} C_6H_5CO & NOCOCH_3 \\ \quad | & \quad \| \\ \multicolumn{2}{l}{C_6H_5C{=}CHCC_6H_5} \end{array}$$

LX



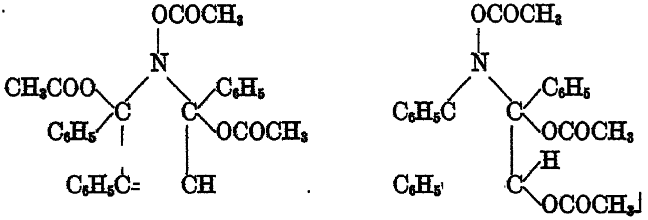
LXII

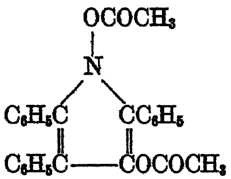


LXIV

Acetylation of LV by acetic anhydride produces LXI; the reaction is complicated but it apparently involves an initial 1,3-addition to the nitrone system, which is followed by a 1,3-shift and loss of acetic acid. The structure of LXI follows from its stepwise reduction through LXII to LVII.

LV

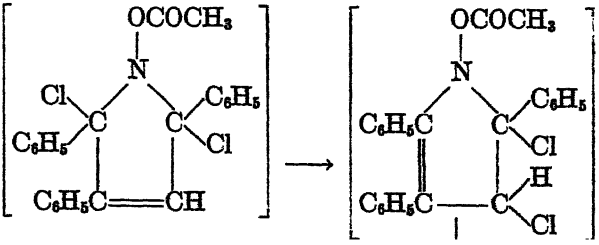


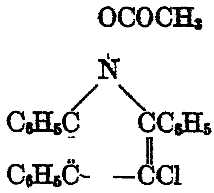


LXI

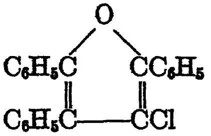
Acetylation of LV by acetyl chloride leads to three products. One of these is LXIII, which is also formed by a series of reactions beginning with 1,3-addition. The structure of LXIII follows from its stepwise reduction through LXIV to LVII. The other two substances produced by the action of acetyl chloride upon LV are the chlorofuran (LXV) and diacetohydroxamic acid (LXVI). These two substances do not arise by a reaction of the chloropyrrole (LXIII), for the latter is unaffected by acetyl chloride.

LV

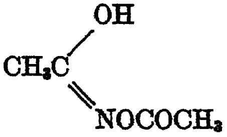




LXIII



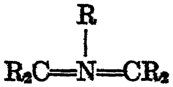
LXV



LXVI

Hence the source of LXV and LXVI must be the open-chain oxime (LIII) or its acetate (LX), both of which give LXV and LXVI on treatment with acetyl chloride, while the only source of LXIII must be the nitrone (LV); these facts indicate that there is an equilibrium established between LV and LIII, or that LV and LIII are at least partly interconvertible, in the presence of acetyl chloride.

VIII. THE NITRENES OF STAUDINGER[3] (340):

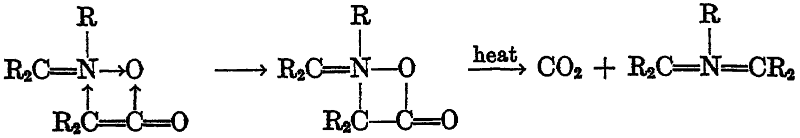


$$R_2C{=}\overset{\overset{R}{|}}{N}{=}CR_2$$

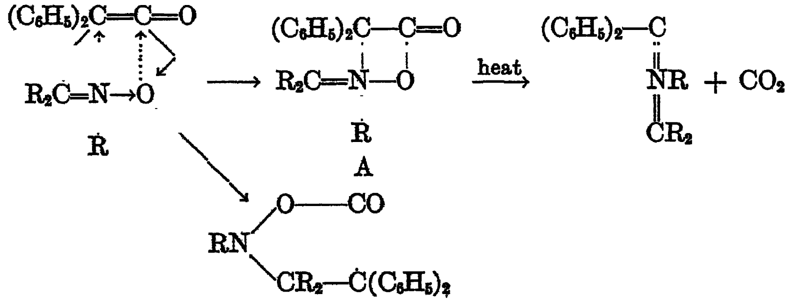
These compounds are not nearly so well known as the other compounds containing 1,3-systems. They are obtained by heating the addition products obtained from ketenes and nitrones, whereupon carbon dioxide is eliminated:

---

[3] As stated later, it is very difficult to set up reasonable electronic formulas for the nitrenes; indeed, in view of the modern electronic concepts of the structures of organic compounds, one would be inclined to regard Staudinger's representations of these compounds with some suspicion, even after transforming them into electronic formulas, for a semipolar valence must, of necessity, be involved. While the proof



In some cases the nitrene is not the only product of the reaction between a nitrone and diphenylketene, for the two substances can combine in two different ways. Addition of the N→O group to the double bond of the ketene (shown by the dotted arrows) produces the intermediate A which, when heated, decomposes (like certain β-lactones) into carbon dioxide and the nitrene. The other product (B) is obtained by a 1,3-addition of the ketene to the nitrone (shown by the unbroken arrows). This product is stable, survives the heating which decomposes A, and is recovered from the mother liquors obtained from the crystallization of the nitrene.



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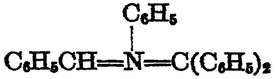
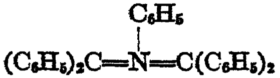
of this article was being read, there appeared a paper by Taylor, Owen, and Whittaker (354a) in which the whole question as to the structure of these compounds is reopened. The evidence which led Staudinger to choose the nitrene formula for "tetraphenylnitrene" was (*a*) the compound was colored and (*b*) reduction gave an amine, which was tertiary, since it could not be transformed into a nitroso compound. Taylor, Owen, and Whittaker have repeated Staudinger's synthesis of the nitrene, and they find that the substance is colorless when pure; moreover, on reduction it is readily transformed into an amine which does give a nitroso compound, therefore the amine is not tertiary. Hence they regard the "nitrene" as a cyclic imine analogous to formula VI (page 270), although they were unable to synthesize the imine by an independent method. The question as to the structure of the "nitrenes" must therefore be regarded as still unsettled, although the most recent structural evidence, together with the difficulties involved in transforming the nitrene formulas into electronic structures, makes it probable that these substances are, in reality, cyclic compounds.

In this way Staudinger prepared the pale yellow *N*-phenyltriphenylnitrene (I), the yellow *N*-phenyltetraphenylnitrene (II), and the green, very unstable diphenylenediphenyl-*N*-phenylnitrene (III).



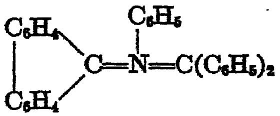
$$C_6H_5CH{=}\overset{\overset{\displaystyle C_6H_5}{|}}{N}{=}C(C_6H_5)_2$$

I



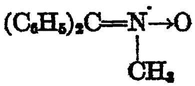
$$(C_6H_5)_2C{=}\overset{\overset{\displaystyle C_6H_5}{|}}{N}{=}C(C_6H_5)_2$$

II



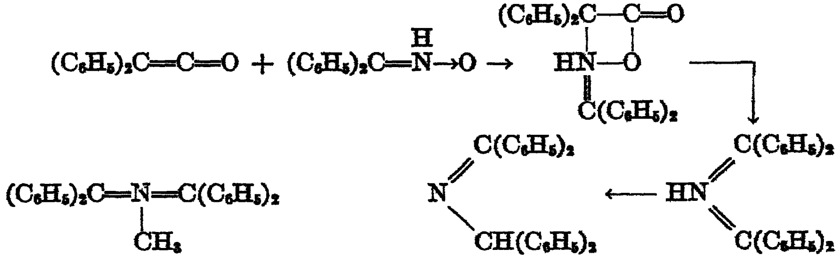
III

No nitrenes could be prepared in which the nitrogen atom held an aliphatic group. Diphenyl-*N*-methylnitrone,



$$(C_6H_5)_2C{=}\underset{\underset{\displaystyle CH_3}{|}}{N}{\rightarrow}O$$

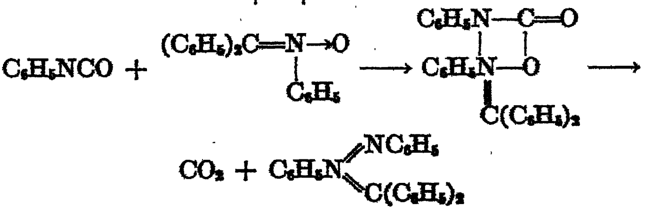
was inert to diphenylketene and none of the expected product (IV) was found. However, benzophenone oxime did react (in the tautomeric nitrone form) with diphenylketene to give not the nitrone, but a rearrangement product of it (V).



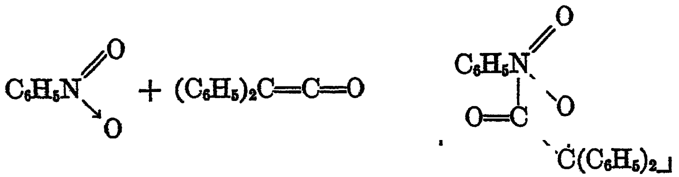
IV

V

The addition of phenyl isocyanate to nitrones was expected to take a course similar to that of the addition of ketenes to nitrones, but no products containing the grouping $>C{=}\underset{|}{N}\overset{\rightarrow}{=}\underset{|}{N}$ could be isolated.



Staudinger regards the nitrenes as nitro compounds in which both oxygen atoms have been replaced by methylene residues. However, nitrenes cannot be prepared by addition of 2 moles of diphenylketene to a nitro compound with subsequent elimination of carbon dioxide, for this reaction leads to a ketone and an isocyanate:



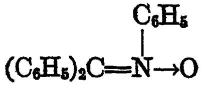
$$(C_6H_5)_2CO + C_6H_5NCO + O$$

The nitrenes prepared by Staudinger were nicely crystalline substances; they showed no tendency to polymerize. They are more deeply colored than the nitrones, but not so deeply colored as the ketenes. Of the six compounds below, containing twinned double linkages, the ketenes are the most deeply colored.

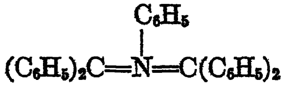
$O{=}C{=}O$ (colorless)

$(C_6H_5)_2C{=}C{=}C(C_6H_5)_2$ (colorless)

$C_6H_5NO_2$ (almost colorless)



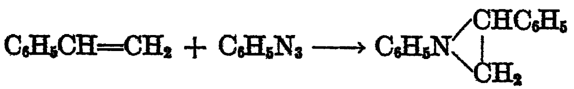
$(C_6H_5)_2C{=}N(C_6H_5){\rightarrow}O$ (pale yellow)

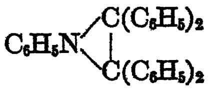


$(C_6H_5)_2C{=}N(C_6H_5){=}C(C_6H_5)_2$ (yellow)

$(C_6H_5)_2C{=}C{=}O$ (orange-red)

It is very difficult to set up electronic formulas for the nitrenes; they may be three-membered rings such as VI, for such compounds were prepared by Wolff (384) by the action of azides upon other unsaturated compounds, or the nitrenes may even be some other rearrangement product such as VII, although the 1,3-additions which they show do not agree with such a structure.



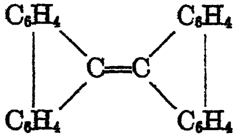


VI

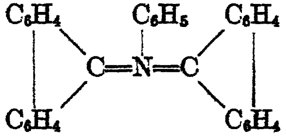
$$(C_6H_5)_2C{=}NC(C_6H_5)_3$$

VII

Staudinger thinks the compounds are really nitrenes, chiefly because of the color and because the reaction between "Graebe's hydrocarbon" (VIII) and phenyl azide led to nitrogen and a green compound corresponding to a nitrene (IX).

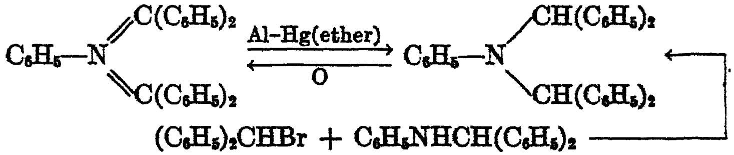


VIII

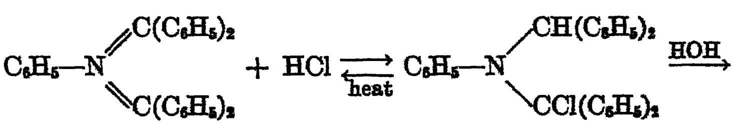


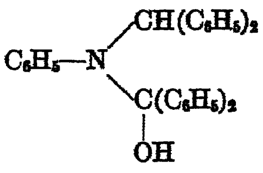
IX

Besides the color, the few known reactions of these substances indicate the nitrene formula; they are 1,3-additions, as would be expected from substances containing the nitrene linkage. Thus reduction leads to tertiary amines, and the structure of the amine obtained by reduction of pentaphenylnitrene was proved by an independent synthesis. The reduction product can be oxidized back to the nitrene by a number of oxidizing agents.

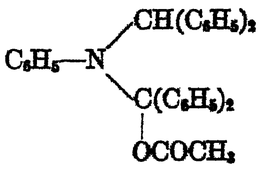


The addition of gaseous hydrochloric acid was formulated in a similar manner; the reaction could be reversed by heating, but the product was easily and quantitatively hydrolyzed to give X:





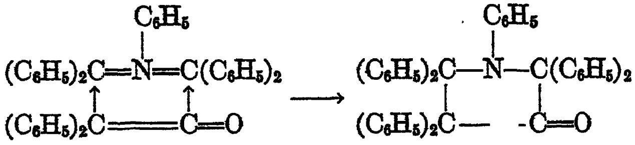
X



XI

When boiled with acetic acid for a long time, pentaphenylnitrene gives a white, crystalline acetate, probably XI. The nitrene in chloroform solution adds one molecule of bromine or chlorine to form a colored, unstable product. Only part of the halogen is removed from this product by treatment with alkali.

Among the unsaturated compounds, only diphenylketene reacted with nitrenes by addition. Only one molecule of the ketene added, and though the structure of the addition product was not determined, it is probably formed by a direct 1,3-addition. The reaction is reversed by heating.



$$\begin{array}{c} (C_6H_5)_2C{=}\overset{\overset{C_6H_5}{|}}{N}{=}C(C_6H_5)_2 \\ \uparrow \qquad\qquad \uparrow \\ (C_6H_5)_2C{=}{=}{=}C{=}O \end{array} \longrightarrow \begin{array}{c} (C_6H_5)_2C{-}\overset{\overset{C_6H_5}{|}}{N}{-}C(C_6H_5)_2 \\ | \qquad\qquad | \\ (C_6H_5)_2C{-}\quad{-}C{=}O \end{array}$$

IX. THE AZOXY COMPOUNDS: $RN{=}\overset{\overset{O}{\uparrow}}{N}R$

The chemistry of the azoxy compounds has been reviewed recently by Bigelow (47).

These compounds contain the system $-N{=}\overset{\overset{O}{\uparrow}}{N}-$; they are, however, the most stable of all compounds containing the 1,3-system, and it is doubtful whether any reaction of the azoxy compounds is known which can be interpreted as a 1,3-addition with any certainty. This may be due to the fact that the system is relatively unreactive, hence intermediate products resulting from 1,3-additions have been overlooked; this in turn is probably due to the fact that in recent years the chief interest in the azoxy compounds has been centered in their isomerism, rather than in the chemistry of the group $-N{=}\overset{\overset{O}{\uparrow}}{N}-$ (11, 165, 246, 380, 9).

Azoxybenzene was discovered by Zinin (389) as an intermediate product in the reduction of nitrobenzene with alcoholic potassium hydroxide. It is the most stable of all of the reduction products of the nitro compounds. Azoxybenzene is not attacked by dilute acids or bases; it is resistant to the action of oxidizing agents and fairly stable toward reducing agents; it is not attacked by hydroxylamine or by phenylhydrazine and it is inert toward many other reagents. Since the characteristic grouping of the azoxy compounds is one which would be expected to undergo 1,3-additions, it is likely that a careful reinvestigation of certain of the reactions of these compounds would result in the isolation of primary products formed by this mode of addition.

SUMMARY

The purpose of this review has been to present a summary of what is known about 1,3-systems which are capable of undergoing 1,3-additions and to bring to the attention of chemists the possibilities which these compounds offer as fields of research when considered from this point of view.

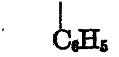
TABLE 1

	I CARBON DIOXIDE $O{=}C{=}O$	II ALDO KETENES $RCH{=}C{=}O$	III KETO KETENES $R_2C{=}C{=}O$	IV ALLENES $R_2C{=}C{=}CR_2$	V ALKYL ISOCYANATES $RN{=}C{=}O$
Hydrogen compound..	$O{=}\underset{\underset{H}{\mid}}{N}{=}O$ Nitrous acid	$RCH{=}\underset{\underset{H}{\mid}}{N}{=}O$ Tautomeric aldoximes	$R_2C{=}\underset{\underset{H}{\mid}}{N}{=}O$ Tautomeric ketoximes	$R_2C{=}\underset{\underset{H}{\mid}}{N}{=}CR_2$ [Nitrenic "hydrocarbons"]	$RN{=}\underset{\underset{H}{\mid}}{N}{=}O$ Diazo hydrates, tautomeric form
Alkyl compound......	$O{=}\underset{\underset{R}{\mid}}{N}{=}O$ Nitro compounds	$RCH{=}\underset{\underset{R}{\mid}}{N}{=}O$ Aldo nitrones	$R_2C{=}\underset{\underset{R}{\mid}}{N}{=}O$ Keto nitrones	$R_2C{=}\underset{\underset{R}{\mid}}{N}{=}CR_2$ Nitrenes*	$RN{=}\underset{\underset{R}{\mid}}{N}{=}O$ Azoxy compounds
Acids.........	$O{=}\underset{\underset{OH}{\mid}}{N}{=}O$ Nitric acid	$RCH{=}\underset{\underset{OH}{\mid}}{N}{=}O$ Aldo nitronic acids (iso nitro compounds)	$R_2C{=}\underset{\underset{OH}{\mid}}{N}{=}O$ Keto nitronic acids (iso nitro compounds)	$R_2C{=}\underset{\underset{OH}{\mid}}{N}{=}CR_2$ [Nitrenic acids]	$RN{=}\underset{\underset{OH}{\mid}}{N}{=}O$ Nitramines (tautomeric form)

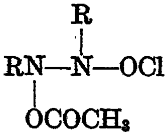
* See the note at the beginning of the section on nitrenes. These substances are probably cyclic compounds.

As Staudinger and Miescher (345) pointed out some time ago, all of the compounds containing these 1,3-systems can be regarded as derived from nitric and nitrous (tautomeric form) acids in the same way that ketenes, allenes, etc., may be regarded as derivatives of carbon dioxide. This is shown in table 1; the compounds in brackets are still unknown.

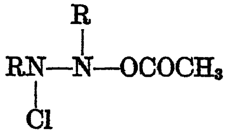
A great many representatives of these compounds are known, some only in tautomeric forms, but most of them were made either for purposes of studying phases of isomerism and tautomerism or in attempts to obtain compounds in which nitrogen was joined by five valences to carbon. Most of this work was done before the development of the modern electronic theory of valence and its application to organic reactions. Thus when Pfeiffer (284) coined the word "nitrone" for certain of these compounds, he had in mind certain similarities between the nitroso group and the carbonyl group; he did not emphasize that the real nitrone group was not the nitroso group, but the group $\rangle C{=}\underset{|}{N}{\rightarrow}O$ and that it was this group, terminated by carbon and oxygen which, in many of its reactions, behaved as an extended carbonyl group. That the system could behave in this way is due of course to the variable valence of nitrogen, which makes possible the existence of stable compounds containing this linkage and enables these compounds to react as though the nitrogen were not there. There are apparently limits to the analogies shown in table 1, however, for it seems that real 1,3-additions occur only when at least one end of the system terminates in a carbon atom. Thus no 1,3-additions of the azoxy compounds are known with certainty, nor do the nitro compounds undergo this type of reaction, so far as is known. It is not difficult to understand this, for most of the reagents which add to heterogeneous unsaturated linkages are of the kind in which one of the parts added must almost necessarily become attached to carbon in order to form stable compounds. Thus acetyl chloride, which adds as a chlorine atom and an acetyl group, can readily form stable products by adding to a nitrone, for the acetyl group can become attached to oxygen and the chlorine atom to carbon; or this reagent could add to a nitrene, in which both groups become attached to carbon; but it could not form a stable product by adding to nitrobenzene to give I, or to an azoxy compound to give II or III, although the latter might conceivably be stable enough to be isolated under special conditions.


$ClO\underset{\underset{C_6H_5}{|}}{N}{-}OCOCH_3$

I


$R\underset{\underset{OCOCH_3}{|}}{N}{-}\overset{\overset{R}{|}}{N}{-}OCl$

II

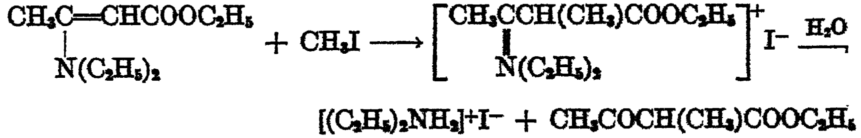

$R\underset{\underset{Cl}{|}}{N}{-}\overset{\overset{R}{|}}{N}{-}OCOCH_3$

III

Nor can organometallic compounds be used with any certainty of obtaining definite results, for in order to obtain the primary products the addition must be so rapid that other reactions (reduction, condensation, etc.) do not occur to any appreciable extent and the primary product must itself be stable toward the organometallic compound. This is shown by the fact that the reactions between Grignard reagents and tertiary nitro compounds or azoxy compounds are very complicated and consist to a large extent in reduction. The one process which is apparently applicable to all these 1,3-systems is reduction, but in this case the results are not decisive as to the mode of addition because the primary products undergo tautomeric changes which cannot be followed. But it would seem that by introducing 1,3-systems into new sorts of structures it might be possible to obtain compounds in which the addition of many reagents could be definitely followed by isolating stable intermediates. An example of this line of attack is found in the study of the cyclic nitrones by Kohler and Blatt, in which the carbon and nitrogen atoms of the nitrone system were included as part of a ring. The isatogens likewise offer this same structural modification for in these compounds part of the nitrone system is likewise included in a ring.

The 1,3-systems also offer interesting possibilities for the study of conjugation. In the isatogens the nitrone system is conjugated with a carbonyl group, but as yet no 1,5-additions of these compounds have been reported. The isatogens show some similarities with the quinones—they are deeply colored, form "quinhydrones" etc.—and Pfeiffer called them "meta-quinoids." The analogy is not valid for if one properly considers the whole nitrone system as equivalent to the carbonyl group, then these compounds are not meta-quinoids, but are ortho-quinoids, and as such the analogy becomes valid and complete and is a striking piece of evidence that the nitrone system really is, in effect, an extended carbonyl group. It would be interesting to build a "para-isatogen," that is, the vinylog of an isatogen, for it would be predicted that such a compound would exhibit many of the properties of *p*-quinones.

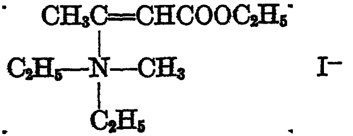
A study of these systems which undergo 1,3-additions may lead to results which can be applied in other fields. For example, Robinson in 1916 (306) alkylated β-diethylaminocrotonic ester with methyl iodide. The products were methylacetoacetic ester and diethylammonium iodide, and Robinson formulated the reaction as a primary 1,3-addition, as follows:



$$\begin{array}{l} CH_3C{=}CHCOOC_2H_5 \\ \quad | \\ \quad N(C_2H_5)_2 \end{array} + CH_3I \longrightarrow \left[\begin{array}{l} CH_3CCH(CH_3)COOC_2H_5 \\ \quad \| \\ \quad N(C_2H_5)_2 \end{array}\right]^+ I^- \xrightarrow{H_2O}$$

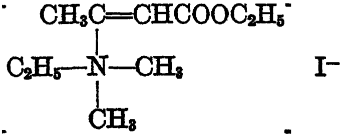
$$[(C_2H_5)_2NH_2]^+I^- + CH_3COCH(CH_3)COOC_2H_5$$

While this reaction could be regarded as an addition centering entirely around the nitrogen atom, followed by a migration of the methyl group, such a formulation would involve a preferential migration of the methyl group from an intermediate such as A.



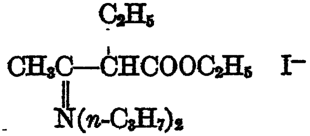
$$\left[\begin{array}{c} CH_3C{=}CHCOOC_2H_5 \\ | \\ C_2H_5{-}N{-}CH_3 \\ | \\ C_2H_5 \end{array}\right] I^-$$

A



$$\left[\begin{array}{c} CH_3C{=}CHCOOC_2H_5 \\ | \\ C_2H_5{-}N{-}CH_3 \\ | \\ CH_3 \end{array}\right] I^-$$

B



$$\begin{array}{c} C_2H_5 \\ | \\ CH_3C{-}CHCOOC_2H_5 \quad I^- \\ \| \\ N(n\text{-}C_3H_7)_2 \end{array}$$

C

In a recent study, Lauer and Lones (205) have subjected dimethylaminocrotonic ester to the action of ethyl iodide. As the intermediate (B) corresponding to A has both methyl and ethyl groups attached to the nitrogen, the former should rearrange as does the latter, and the product should be the same from both A and B. Actually the second reaction gave ethylacetoacetic ester and dimethylammonium iodide. A number of other alkylations of this type were studied by Lauer and Lones, and in every case the R group of the alkyl iodide was the one which was found present in the final product, the alkylated acetoacetic ester. When β-di-*n*-propylaminocrotonic ester was subjected to the action of ethyl iodide, the intermediate product (C) was actually isolated and shown to give ethyl acetoacetic ester upon hydrolysis. These results lend strong support to Robinson's mechanism for the action of alkyl iodides upon β-dialkylaminocrotonic esters and exclude the possibility that the mechanism involves addition at the nitrogen atom alone. Robinson's mechanism can of course be transferred to the ordinary alkylation of acetoacetic esters; here oxonium salts would be the intermediates.

In the case of the nitrones and similar systems, the 1,3-additions involve an (inner) ion reacting with a non-ionic substance to give a non-ionic product; in the alkylation of the dialkylaminocrotonic esters, the 1,3-additions involve two non-ionic substances reacting to produce an ion. In the former case, the element with the variable "valence" is in the middle of the 1,3-system; in the latter case, it is at one end of the system.

Some of the material covered by this review has for a number of years formed a part of an advanced course in organic chemistry given by the author for graduate students, but the whole field of 1,3-systems formed the subject for discussion and presentation before the Organic Seminar at the University of Minnesota during the spring quarter of 1935. The author has made use of the papers presented by the members of the seminar as follows: Mr. W. B. Pings, "Aliphatic Diazo Compounds and Azides"; Mr. L. I. Hansen, "*N*-Ethers of Oximes"; Mr. F. Schmalz, "Isatogens"; Mr. Paul Johnson, "Isoxazoline Oxides"; Mr. H. Hochman, "Nitrenes"; and Mr. J. A. Anthes, "Azoxy Compounds." The author is particularly indebted to Mr. R. W. Raetz, who typed the manuscript and compiled the bibliography.

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THE CHEMISTRY OF FLUORENE AND ITS DERIVATIVES[1]

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[1] This paper is based on a thesis submitted by George Rieveschl, Jr., to the Faculty of the College of Liberal Arts of the University of Cincinnati in partial fulfillment of the requirements for the B. A. degree with High Honors in Chemistry, June, 1937.

The thesis was awarded the Henry Hochstetter Prize on nomination by the Cincinnati Section of the American Chemical Society for the best senior thesis in Chemistry or Chemical Engineering.

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I. INTRODUCTION

The hydrocarbon fluorene has been known for seventy years, yet the amount of investigation that has been devoted to it is small in comparison with that devoted to other hydrocarbons such as anthracene or phenanthrene. In the case of fluorene there has been no sudden stimulus to intense research such as the celebrated alizarin synthesis gave to the study of anthracene. The chemistry of phenanthrene is at this moment undergoing the same phenomenal development, because the chemistry of such biologically significant compounds as sex hormones, carcinogenic substances, and the sterols is basically the chemistry of phenanthrene. Although investigation in the fluorene field has progressed at a relatively slow rate, the result has been a significant amount of literature which is indeed both varied and substantial.

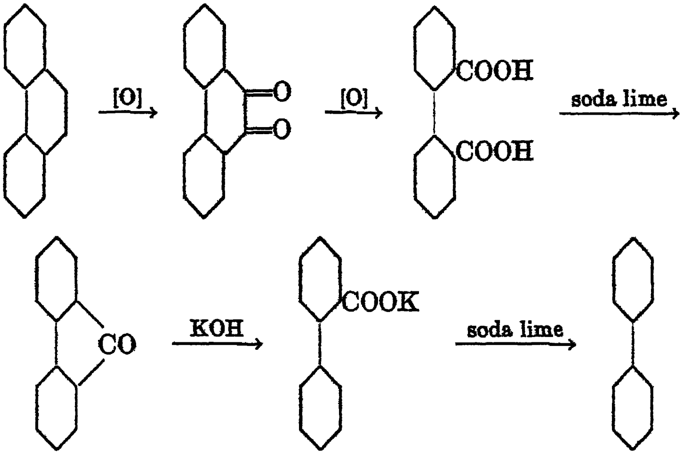
As far as we have been able to determine A. E. Everest's (91) book, published in 1927, contains the only general survey of the chemistry of fluorene. In view of the important developments which have occurred in the last ten years we have attempted to present here a comprehensive and critical discussion of the present knowledge of fluorene and its compounds. Some emphasis has been placed upon general methods of synthesis and cases of practical applicability. In addition, we have endeavored to make suggestions for future research.

II. THE DISCOVERY OF FLUORENE AND THE ELUCIDATION OF ITS STRUCTURE

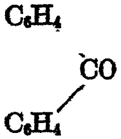
The chemistry of fluorene begins at a comparatively early date in the history of organic chemistry. During his memorable researches on the pyrogenetic hydrocarbons at the Collège de France in 1867, Marcellin Berthelot (29) isolated a new substance from the fraction of crude anthracene oil boiling between 300° and 310°C. He recrystallized the vividly fluorescent material from boiling alcohol and obtained white fluorescent laminae, which melted at 113°C. Berthelot was so impressed by the beautiful fluorescence, more pronounced than that of anthracene, that he gave the substance the name "Fluorène." He also identified fluorene as a product from the decomposition of retene. He described its odor as being "insipid, sweetish, and at the same time distressing to breathe." Berthelot established the difference between fluorene and all other hydrocarbons known at that time by an examination of the physical properties and an elementary analysis, the results of which he reported as follows: carbon, 93.5–94.0 per cent; hydrogen, 6.2–6.5 per cent.[2]

The discovery of phenanthrene in 1872 by Fittig and Ostermayer (102) and independently in the same year by Graebe (125) played an important part in the prompt elucidation of the constitution of fluorene.

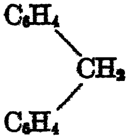
Fittig and Ostermayer (103) in their investigation of phenanthrene carried out the degradation shown below, leading to the known biphenyl.



The compound resulting from the action of soda lime on the then unknown diphenic acid was rightly interpreted as being biphenylene ketone. Later they also obtained biphenylene ketone from phenanthraquinone by treatment with aqueous potassium hydroxide; they reported a melting point of 83.5–84.0°C. Fittig (99) distilled the biphenylene ketone with zinc dust and found that it was reduced to a substance crystallizing in white plates and melting at 113–114°C. He regarded this compound as biphenylene-methane, as shown below.



$$\begin{matrix} C_6H_4 & \\ & \diagdown CO \\ C_6H_4 & \diagup \end{matrix}$$



$$\begin{matrix} C_6H_4 & \\ & \diagdown CH_2 \\ C_6H_4 & \diagup \end{matrix}$$

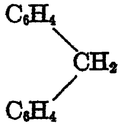
Graebe (126), using the biphenylene ketone of Fittig, carried out the reduction with red phosphorus and hydriodic acid and obtained the same hydrocarbon.

---

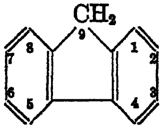
[2] A calculation of carbon and hydrogen from the formula $C_{13}H_{10}$ gives 93.9 per cent carbon and 6.1 per cent hydrogen.

Barbier (13), who had intensively investigated fluorene, observed that the compound obtained by the oxidation of fluorene with potassium dichromate and sulfuric acid was identical with the biphenylene ketone of Fittig and Ostermayer. Later Barbier (15) improved Berthelot's method of isolation of fluorene from coal tar and succeeded in obtaining large quantities of it. His analyses showed that it could be represented by the formula $C_{13}H_{10}$. He regarded fluorene as "biphenyl in which two atoms of hydrogen are replaced by an equal volume of methylene," for on treating fluorene with red-hot lime he obtained biphenyl. It can be easily seen from the work of Barbier that he was relatively certain of the structure of fluorene.

In 1878 Fittig and Schmitz (104) reported that the biphenylenemethane previously obtained by Fittig from biphenylene ketone was identical with fluorene obtained by Berthelot and Barbier. They prepared the picrate and the dibromo derivative from their own biphenylenemethane and found that these compounds were identical with those prepared by Barbier from fluorene isolated from coal tar. The structural formula could then be represented with certainty as[3]



or



Barbier in his experiments purified fluorene by preparing the picrate and then adding ammonia. The resulting fluorene melted at 113°C. and possessed the beautiful violet fluorescence which so impressed Berthelot. However, in 1883 Hodgkinson and Matthews (143) showed that the fluorescence was due to the presence of some impurity which was removed by recrystallization from glacial acetic acid or by sublimation over potassium carbonate. The fluorescence is thought to be due to the presence of rubene derivatives.

III. FLUORENE AND FLUORENONE

Fluorene when pure is a dazzling white substance crystallizing in flakes from alcohol. It is fairly soluble in hot alcohol, more so in acetic acid, carbon disulfide, ether, and benzene, and insoluble in water. DeCarli (65) determined the solubility of fluorene in liquid sulfur dioxide (24 g. per 100 g. of sulfur dioxide) and also in liquid ammonia, in which it was practically insoluble. Glacial acetic acid (143) was found to be one of the best solvents for fluorene and its derivatives.

---

[3] The system of numbering shown has been adopted internationally.

Various investigators have reported slightly different melting points for fluorene. Mortimer and Murphy (211), after careful purification, gave the melting point as 114.2°C. By recrystallization from hot glacial acetic acid we have obtained samples which consistently melt at 113–114°C. Carnelly (38) reported an isomeric form of fluorene melting at 118°C. The boiling point is 298°C. (211). Mortimer and Murphy have also determined the vapor pressure at various temperatures (table 1). The density of fluorene, $d_4^{17.9°}$, is 0.91648 (43).

Vanscheidt (322) described a colorimetric test for hydrocarbons containing the group $(C{=}C)_2CH_2$, such as exists in cyclopentadiene, indene, and fluorene. These compounds in pyridine or acetone give colored solutions with alcoholic potassium hydroxide. The reaction is evidently not due to the active methylene hydrogen in these compounds, for other closely related compounds such as diphenylmethane and triphenylmethane do not give the reaction.

TABLE 1

Vapor pressure of fluorene

TEMPERATURE	VAPOR PRESSURE	TEMPERATURE	VAPOR PRESSURE
°C.	*mm.*	*°C.*	*mm.*
150	11.9	230	155.0
160	17.4	240	202.0
170	24.9	250	259.0
180	34.8	260	332.0
190	48.1	270	419.0
200	65.4	280	527.0
210	88.6	290	656.0
220	120.4	300	808.0

The isolation of fluorene from coal-tar fractions in which it is present to the extent of 1.6 per cent is, at the present time, effected through the formation of a potassium derivative at a high temperature (300°C.). Separation is easily accomplished, and subsequent treatment with water regenerates fluorene (113, 327, 330). Sodamide has also been used in this separation (184, 331).

A number of molecular addition products with fluorene have been reported. They are summarized in table 2.

McEwen (195) has recently studied the behavior of fluorene and some of its derivatives as an example of an extremely weak acid. Fluorene after exposure to ultraviolet light from a quartz-mercury lamp shows phosphorescence followed by a photochemical effect (161).

Fluorenone, the oxidation product of fluorene, is a beautiful yellow crystalline material[4] melting at 83–84°C. and boiling at 341°C. (152). In preparing fluorenone by the method of Huntress, Herschberg, and Cliff (using sodium dichromate in acetic acid) we have obtained it in rhombic crystals over 3 cm. in length. The solubility of fluorenone has been determined in various solvents (table 3).

TABLE 2

Molecular addition products of fluorene

REAGENT	RATIO OF MOLES OF FLUORENE TO MOLES OF REAGENT	MELTING POINT	COLOR AND FORM
		°C.	
Picric acid (104)	1:1	80–82	Red needles
2,4-Dinitrochlorobenzene (35)	1:1	39 (approx.)	Straw yellow
Picramide (88)	1:1	127.5	Yellowish brown
Tetryl (89)	1:1	77.5 (decomp.)	
Trinitro-*m*-cresol (63)	1:1	109 (explodes at 421)	Deep yellow
3,5-Dinitro-*p*-hydroxybenzoic acid (210)	1:2	218–221 (closed tube)	Yellow powder
1,3,6,8-Tetranitronaphthalene (222)	1:2	154–155	Brownish needles
s-Trinitrobenzene (177, 306)	2:3	105	Golden yellow plates
Trimesic acid trichloride (23)	1:1	75–77	Yellow
3,5-Dinitrobenzonitrile (23)	1:2	128–130	Yellow
2,7-Chlorophenanthraquinone (140)			Deeply colored melts
1,2,3,4,5,6,7-Heptachloroanthraquinone (140)			
1-Nitroanthraquinone (140)			

TABLE 3

Solubility of fluorenone

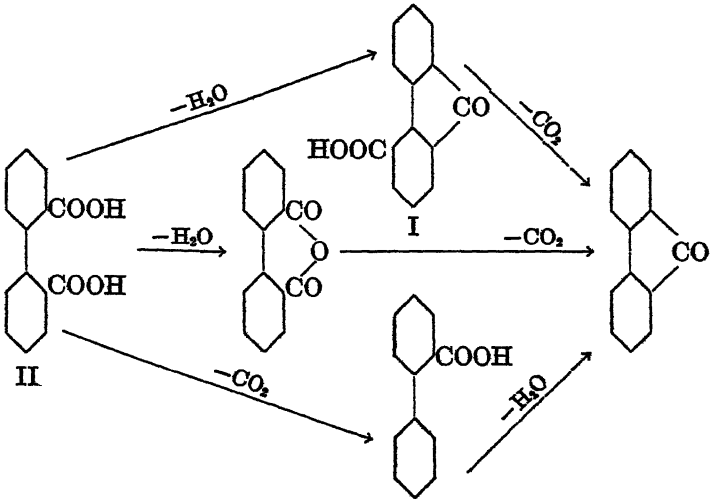
SOLVENT	GRAMS PER GRAM OF SOLVENT AT 22°C.
Alcohol (95 per cent)	0.075
Carbon tetrachloride	0.19
Ether	0.31
Benzene	0.68

---

[4] Kerp (Ber. 29, 228 (1896)) reported a pseudo form, melting at 85°C. and forming dark red crystals. Although Stobbe (Ber. 44, 1481 (1911)) has confirmed this observation, it would seem to require further investigation.

Postovski and Lugovkin (234) have shown that fluorene on oxidation with selenium oxide gives only 5 per cent of fluorenone. Under the same conditions diphenylmethane gives 87 per cent of benzophenone, indicating the greater resistance of fluorene to oxidation owing to the linking of benzene rings. Courtot (53) used solutions of potassium permanganate at room temperature to oxidize fluorene and derivatives to the corresponding fluorenones; the yields were mostly quantitative. Usually the oxidation is carried out with sodium dichromate and acetic acid. This method is suitable for large-scale laboratory production of fluorenone (152).

Huntress, Herschberg, and Cliff (152) also studied the conversion of diphenic acid to fluorenone. As seen by the equations, the transformation may take place in three ways.[5] At 360°C. the conversion was rapid and quantitative. No conclusion as to the mechanism of the reaction could be drawn, because under the same conditions both fluorenone-4-carboxylic acid (I) and diphenic acid (II) gave the same result. These authors recommend their method for the preparation of fluorenone of high purity.



Fluorenone combines with one molecule of perchloric acid to form an oxonium perchlorate of the formula $C_{13}H_8OHClO_4$ (144). This formation of a perchlorate has been suggested as a method for the isolation and identification of ketones, especially in the case of those compounds which fail to yield picrates. Other addition products such as fluorenone zinc chloride (243), fluorenone nitrate (198, 244, 261b), and fluorenone mercuric chloride (4, 198) have been prepared.

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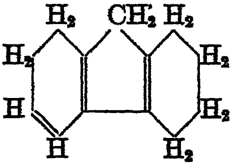
[5] Huntress, Herschberg, and Cliff overlooked the previous preparation by Graebe and Mensching (Ber. 13, 1302 (1880)) of fluorenone from diphenic anhydride by heating.

IV. REDUCTION PRODUCTS OF FLUORENE

Several distinct reduction products of fluorene are known. Guye (135) has reported an octahydrofluorene, $C_{13}H_{18}$, which he obtained along with the decahydrofluorene, $C_{13}H_{20}$, by heating fluorene with phosphorus and hydriodic acid in a sealed tube. Liebermann and Spiegel (185), who used the same method, obtained the perhydro compound, $C_{13}H_{22}$. Decahydrofluorene was also prepared by Schmidt and Mezger (266) with phosphorus and iodine. More careful work by Ipatieff (156) has shown that decahydrofluorene was the chief product of the hydrogenation of fluorene at 290°C. under 120 atm. pressure, and on further treatment with hydrogen at 285°C., under a higher pressure, perhydrofluorene was obtained. Nickel oxide was used as the catalyst.

Sadikov and Michailov (252), in a more recent investigation, studied the hydrogenation of fluorene under pressure in the presence of various catalysts. Osmium proved to be superior to nickel oxide, giving a 78 per cent yield of the decahydro compound and a 22 per cent yield of the perhydro compound. The addition of small amounts of the oxides of cerium and thorium to the osmium catalyst increased the yield of perhydrofluorene to 93 per cent and 100 per cent, respectively. Although nickel oxide by itself proved to be somewhat inefficient, the presence of 1 per cent of cerium oxide brought about a 98.2 per cent yield of perhydrofluorene. The addition of 1 per cent of thorium oxide to the nickel oxide catalyst was surprisingly inefficient; in fact, all of the fluorene was recovered unchanged.

From a "fat" French coal found in the Loire region, Pictet and Ramseyer (229) obtained hexahydrofluorene, $C_{13}H_{16}$, by extraction with benzene. At red heat it was dehydrogenated to fluorene. The fact that hydrogen was given off at high temperatures led these authors to state that this property may be common to other hydrogenated hydrocarbons, thus accounting for the presence of aromatic hydrocarbons in coal tar and hydrogen in coal gas as a result of distillation at ordinary pressure. The following two formulas were proposed:



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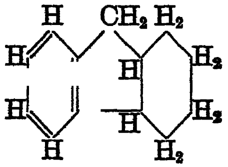
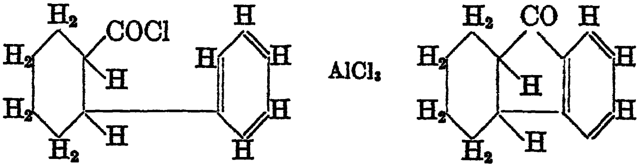


II

An investigation of the dehydration of benzylcyclohexanols by Cook and Hewett (48) led to the synthesis of 1,2,3,4,10,11-hexahydrofluorenone.

2-Phenylhexahydrobenzoyl chloride was treated with aluminum chloride in carbon disulfide at 0°C. Ring closure took place as shown in the following equation:



Reduction with amalgamated zinc and hydrochloric acid gave 1,2,3,4,10,11-hexahydrofluorene (Pictet's formula II). Cook and Hewett reported it to boil at 127°C. at 15 mm. pressure, while Pictet and Ramseyer gave 110–120°C. at 10 mm. pressure. Whether the two products were identical or were structural isomers (I and II) cannot be stated with certainty.

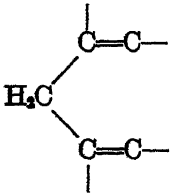
9-Aminohexahydrofluorene was obtained catalytically in two forms from fluorenone oxime (213). The hydrochloride of the α-form melted at 236°C. and the hydrochloride of the β-form at 306°C. The α-form proved to be racemic, resolution being effected with active tartaric acid.

Lebeau and Picon (184) have reported a 9-methyltetrahydrofluorene.

V. GENERAL METHODS OF SYNTHESIS OF DERIVATIVES OF FLUORENE AND FLUORENONE

The synthesis of fluorene and fluorenone derivatives may be considered in two general divisions: first, synthesis by direct substitution in the fluorene molecule itself; second, synthesis through indirect methods from appropriate intermediate compounds.

Fluorene is particularly interesting, owing to the presence of a methylene group which is activated by two pairs of doubly linked carbon atoms. This



has been shown by Thiele (308) to be an excellent illustration of the polar influence of the ethylenic double bond.[6] Examination of the structures of cyclopentadiene (I), indene (II), and fluorene (III) shows that fluorene may be considered as dibenzocyclopentadiene and indene as benzocyclopentadiene.

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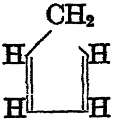
[6] Goss and Ingold (J. Chem. Soc. 1928, 1268) have given an explanation of the reactivity of the methylene group in terms of the electron theory.



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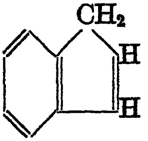
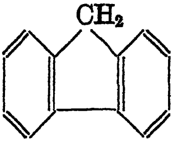
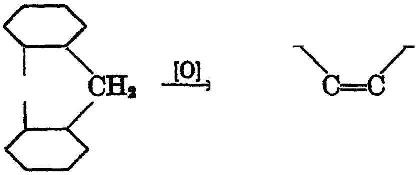


II

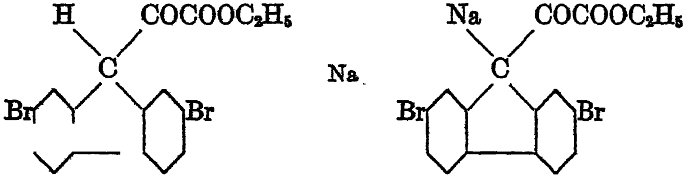


III

Thiele and Henle (311, cf. 310) found that the reactivity of the methylene group in these compounds was in the order cyclopentadiene > indene> fluorene. This was formulated on the basis that the activity of the methylene group decreases as the ethylene groupings of the five-atom ring are rendered inactive by benzene nuclei. The reactivity in fluorene was evidenced by the formation of sodium and potassium derivatives as well as condensations with the carbonyl group (to be considered later). If fluorene in the vapor state is passed over heated lead oxide the red hydrocarbon dibiphenyleneëthylene is obtained, showing the reactivity of the hydrogen atoms in the 9-position (70).



Sieglitz (283) found that, owing to the activity of the 9-hydrogen atom in ethyl 2,7-dibromofluorene-9-oxalate, it could be substituted by sodium and could thus yield a number of derivatives.



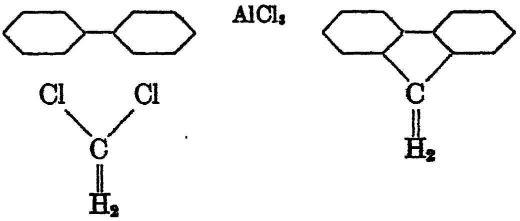
Courtot and Geoffroy (55) found in attempts to introduce hydroxyl groups that alkali fusion of sulfonated fluorenes oxidized the methylene group to give substituted biphenylcarboxylic acids. Fluorenone behaved in a similar manner. Other derivatives also show this transformation and it may be considered a general chemical property of fluorene compounds. This greatly restricts the versatility of these substances.

The study of substituted fluorenones on fusion with alkali has been extended to 1,4-dimethylfluorenone (255).

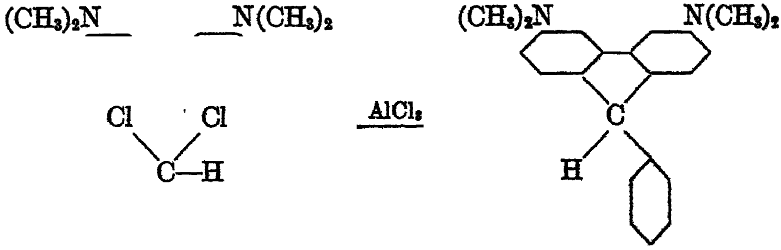
Substitution in the two benzene nuclei of the molecule seems to proceed upon a rather definite plan. Courtot (55), in his extensive investigations of fluorene, showed that chlorine, bromine, nitric acid, and sulfuric acid react in the 2-position. Further substitution leads to 2,7-compounds (250) in all but a few cases. Very little is known of the orientation of trisubstituted derivatives. As a rule, it may be said that present knowledge permits the preparation only of derivatives involving the 2-,7-,and 9-positions by direct substitution. There are a few exceptions such as 2,5-dinitrofluorene, 2,3-diacetylfluorene, and 2-amino-3-nitrofluorene, which have been prepared by direct substitution, and further research might well show others.

Syntheses through indirect methods are numerous and up to the present time have yielded primarily substituted fluorenones; however, there are some cases in which the fluorene derivative has been obtained.

P. Adam (1) at an early date showed that biphenyl and methylene dichloride in the Friedel–Crafts reaction yielded fluorene. The reaction indicated very well the structure of fluorene and its close relationship to biphenyl.

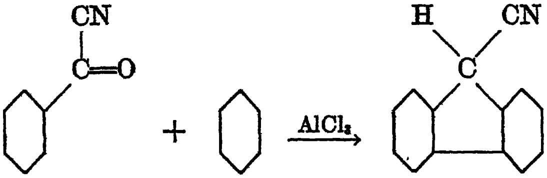


Dutt (78) was probably the first investigator to attempt an extension of this method. By the reaction of 3,3′-tetramethyldiaminobiphenyl and benzal chloride with aluminum chloride in carbon disulfide he obtained 3,6-tetramethyldiamino-9-phenylfluorene.

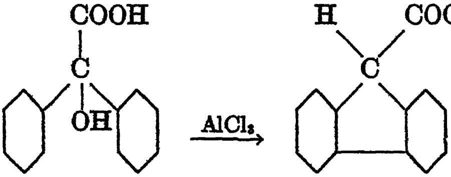


It seems to us that a more intensive investigation into the general applicability of this method would be profitable.

Delacre (69) described the action of ethyl trichloroacetate on benzene in the presence of aluminum chloride to give fluorene-9-carboxylic acid and recommended this method as a general one for the synthesis of fluorene derivatives. As far as we have been able to determine, however, no further investigation has been made. Vörlander (324) obtained 9-cyanofluorene by condensing benzoyl cyanide with benzene in the presence of aluminum chloride, and later (325) prepared fluorene-9-carboxylic acid directly by using benzilic acid in place of benzoyl cyanide (reaction II). When the benzene was replaced with toluene a methyl-substituted fluorene was formed in reaction I.

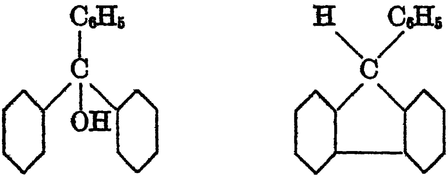


(I)



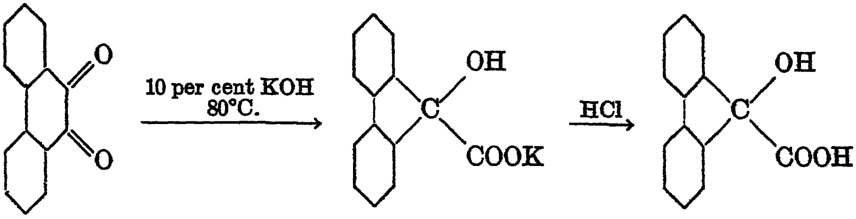
(II)

Kliegl (162) has shown that a similar dehydration to give ring closure occurs on the distillation of triphenylcarbinol with crystalline phosphoric acid to give 9-phenylfluorene.

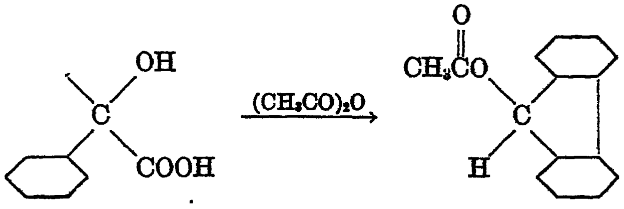


Indirect syntheses yielding substituted fluorenones are more common and have been investigated with some thoroughness in relation to their applicability as general methods. Miller and Bachman (200) have given an excellent critical review of these methods.

The conversion of phenanthraquinone derivatives into derivatives of fluorenone has proved to be one of the most reliable methods. Phenanthraquinone, bearing a structural similarity to open chain α-diketones, undergoes with ease the benzilic acid rearrangement. The product is 9-hydroxyfluorene-9-carboxylic acid or biphenyleneglycolic acid (109, 166, 261a). The latter compound, an α-hydroxy acid, should readily oxidize to fluorenone.



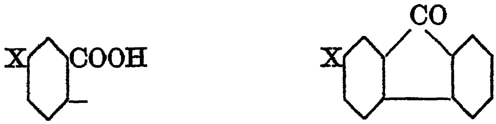
This oxidation was found to occur readily, boiling with water or alkalies in the presence of air being sufficient to bring it about. When 9-hydroxyfluorene-9-carboxylic acid was boiled with acetic anhydride in an atmosphere of hydrogen, 9-fluorylacetate (9-acetoxyfluorene) was formed with the evolution of carbon dioxide (261). Hydrolysis of the latter compound



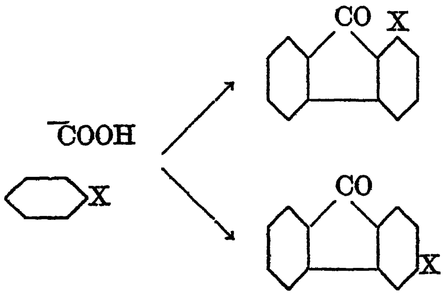
yielded 9-hydroxyfluorene, which could be reduced to fluorene or oxidized to fluorenone. The passage from phenanthraquinone directly to fluorenone was easily accomplished with alkaline permanganate (5).

Schmidt and Bauer (261), using appropriate derivatives of phenanthraquinone, carried out a number of these syntheses. Such compounds as 4,5-dinitrofluorenone, 4-nitro-9-hydroxyfluorene-9-carboxylic acid, and 2-bromo-7-nitrofluorenone were prepared. The nature of the substituents in the phenanthraquinone molecule had a definite effect upon the ease with which the rearrangement took place. Phenanthraquinone itself with 10 per cent potassium hydroxide required a temperature of 80°C. The mononitro derivatives required a temperature of 50–65°C., while with the dinitro compounds the transformation took place at only 15°C. The effect is similar with bromo derivatives, but not to such a marked extent. This method is limited by the fact that many of the desired phenanthraquinones are yet unknown, so the advancement of the chemistry of fluorene by this means depends on the development of phenanthrene chemistry. The rapid expansion of this field, however, in the past ten years is encouraging to investigators interested in fluorene compounds. No investigation has yet been made using the newer knowledge of phenanthraquinone derivatives as a means of preparing new fluorenones.

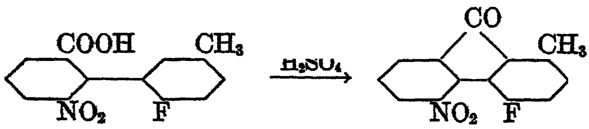
The dehydration of *o*-carboxybiphenyl derivatives constitutes another method which is of value because of the high yields. The ring closure is



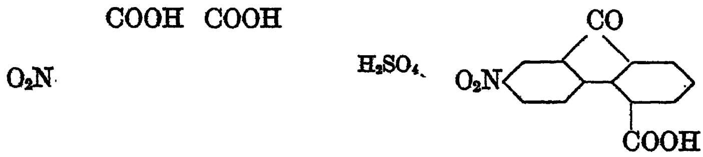
usually effected with concentrated sulfuric acid. A distinct disadvantage is encountered in this method if the substitutent in the second ring is in the meta position, as on ring closure two compounds are possible.



No complications are involved, however, if the substituents are in the first ring or in the ortho and para positions of the second ring. As an example of this reaction, Stoughton and Adams (303) treated 2-nitro-6-carboxy-2′-fluoro-5′-methylbiphenyl with concentrated sulfuric acid and obtained a quantitative yield of 1-methyl-4-fluoro-5-nitrofluorenone.

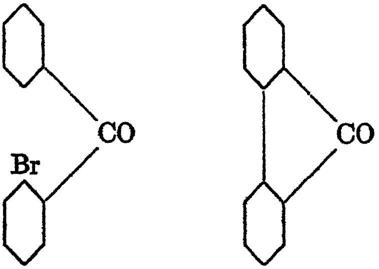


When substituted diphenic acids were used, a substituted carboxyfluorenone was obtained. Moore and Huntress (206a) have prepared 7-nitrofluorenone-4-carboxylic acid from 4-nitrodiphenic acid.



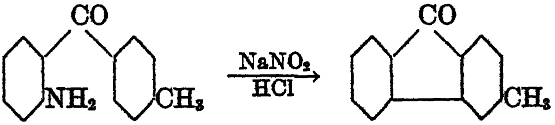
Similarly Fieser (97) prepared 1,6-dimethoxyfluorenone-4-carboxylic acid from 5,5′-dimethoxydiphenic acid.

Fluorenones may also be synthesized from *o*-halogen benzophenone derivatives.

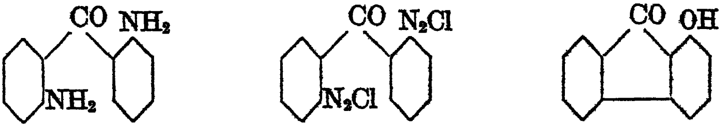


Montagne (203, 204) employed this method in the synthesis of several monobromo and dibromo derivatives of fluorenone. As Miller and Bachman (200) have pointed out, the method possesses disadvantages in that the yields are small, the intermediate compounds difficult to prepare, and rearrangement is possible because of the high temperature required to effect the elimination of halogen acid.

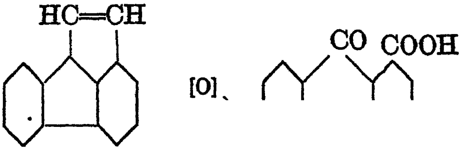
A method, somewhat similar to the preceding one, which has given satisfactory results consisted of the successive diazotization and internal coupling of derivatives of *o*-aminobenzophenone. Ullmann and Mallett (316) prepared 3-methylfluorenone by the action of nitrous acid on *o*-aminophenyl *p*-tolyl ketone.



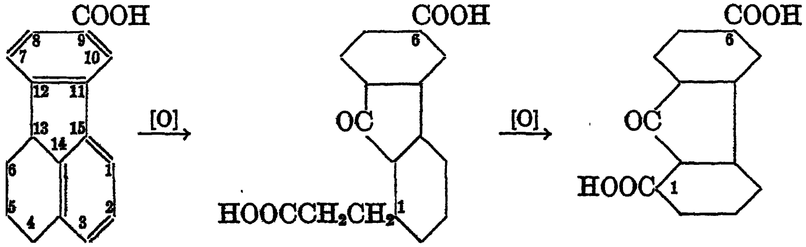
Staedel (290) has given a similar synthesis of 1-hydroxyfluorenone from *o*,*o*′-diaminobenzophenone.



The hydrocarbon fluoranthene offers another road to the synthesis of fluorenone derivatives. Fittig and Gebhard (100) and Fittig and Liepmann (101) showed very early that the oxidation of fluoranthene with chromic acid yielded fluorenone-1-carboxylic acid along with some fluoranthenequinone.



Fieser and Seligman (98) in their work on carcinogenic compounds involving the cholanthrene nucleus have confirmed this result. It is only recently that the extension of this method has been investigated (34a). For example, by oxidizing 4,5,6,13-tetrahydrofluoranthene-9-carboxylic acid (obtained by reducing fluoranthene-9-carboxylic acid with sodium amalgam), 6-carboxyfluorenone-1, β-propanoic acid was obtained, which could in turn be further oxidized to fluorenone-1,6-dicarboxylic acid.



This method presents the same problem encountered with phenanthrene. The chemistry of fluoranthene is still a relatively unexplored field and subsequent development will have a definite effect upon the advancement of fluorene chemistry.

VI. DERIVATIVES[7] OF THE TYPE $(C_6H_4)_2C{=}N$—

Fluorenone is similar in structure to benzophenone, as both contain the carbonyl group situated between two aromatic nuclei. Consequently fluorenone undergoes all the characteristic reactions of an aromatic ketone. It forms an oxime readily and condenses easily with hydrazine derivatives to give hydrazones. A number of these characteristic ketone derivatives are summarized in table 4.

---

[7] The classification of the following compounds is based on the structure of the fluorene molecule. Compounds involving the 9-carbon atom (the methylene group) are described under several structural types (sections VI, VII, and VIII), and compounds involving substitution in the nucleus are classified according to the nature of the substituent. Compounds which fall under both heads will be treated as belonging to the second group. This arrangement should aid in the logical presentation of the subject matter and afford a better view of the chemical properties of fluorene derivatives.

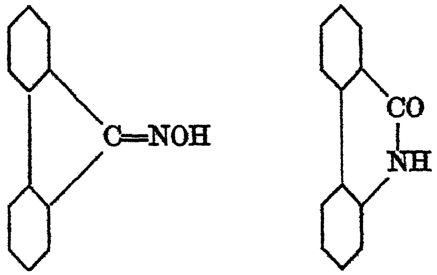
Schmidt and Soll (268) have shown that substitution of the oxygen in the carbonyl group by the oxime group results in a weakening of the coloring power, that is, $>C{=}O$ is a more powerful chromophore than $>C{=}NOH$. Substitution of the oxime hydrogen has some effect on the color, but the effect is less marked.

TABLE 4

Derivatives of fluorenone

COMPOUND	MELTING POINT	COLOR AND FORM
	°*C.*	
Fluorenone oxime (268)	193–194	Light yellow needles
Fluorenone oxime (sodium salt) (268)	Decomposes	Pale yellow
Fluorenone oxime (potassium salt) (268, 344)	Decomposes	Pale yellow
Acetylfluorenone oxime (268)	79	Light yellow
Fluorenone oxime benzoate (268)	179	Pale yellow
Fluorenone oxime methyl ether (268)	145.6	Reddish yellow
Fluorenone phenylhydrazone (120)	151–151.5	Yellow needles
Fluorenone *p*-nitrophenylhydrazone (271, 232)	269 (decomposes)	Orange-yellow needles
Fluorenone hydrazone (336)	149	Light yellow plates
Fluorenone benzoylhydrazone (246)	171	Yellow needles
Fluorenone phenylsemicarbazone (295)	222	

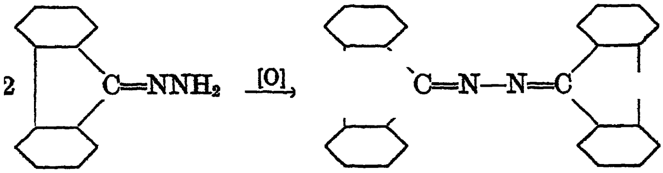
Fluorenone oxime also undergoes the Beckmann transformation on heating with zinc chloride. Pictet and Gonset (228) reported a 30 per cent yield of phenanthridone using this method.



Phenanthridone has also been prepared by Graebe and Schectakow (128) by treating 4-aminofluorenone with dilute potassium hydroxide. Moore and Huntress (206) extended both of these reactions by using substituted fluorenones.

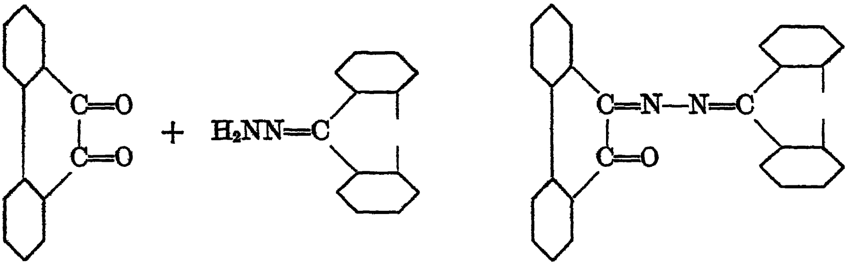
Fluorenone hydrazone takes part in many reactions. Curtius and Kof (60) treated fluorenone hydrazone in absolute alcohol with sodium amalgam and obtained di-9-fluorylamine (cf. 34), $[(C_6H_4)_2CH]_2NH$, in yellow needles melting at 167°C.

Fluorenone ketazine, $(C_6H_4)_2C{=}N{-}N{=}C(C_6H_4)_2$, was prepared by the oxidation of fluorenone hydrazone with quinone or iodine in alcohol. It formed dark red needles with a blue luster, m.p. 259°C. (336).

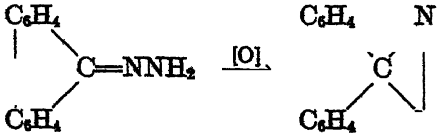


Curtius and Kof (60) have also prepared it either by heating fluorenone hydrazone with fluorenone or by heating fluorenone with hydrazine hydrate.

Other ketazines derived from fluorenone hydrazone have been prepared. Benzalfluorenone ketazine, $(C_6H_4)_2C{=}N{-}N{=}CHC_6H_5$ was prepared by boiling together benzaldehyde and fluorenone hydrazone in alcohol (296). Gerhardt (112) has shown that aromatic keto-hydrazones react with orthoquinones to yield ketazines of the type $R_2C{=}N{-}N{=}R{=}O$. For example, with phenanthraquinone a 45 per cent yield of phenanthraquinofluorenone ketazine, crystallizing in deep brownish needles, was obtained.



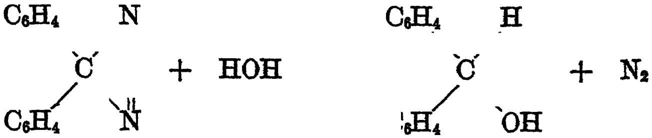
Biphenylenediazomethane (9-diazofluorene) has been obtained by shaking fluorenone hydrazone in benzene with yellow mercuric oxide for 48 hr. (296), and by passing carbon dioxide-free air through a solution of the hydrazone in the presence of sodium (294).



Bennett and Noyes (21) prepared 2-amino-9-diazofluorene from the hydrazone by oxidation in air, using mercury acetamide in an alcoholic solution containing a minute amount of sodium ethylate.

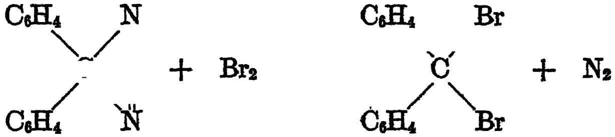
9-Diazofluorene crystallizes in red needles melting at 94–95°C. It is converted into dibiphenyleneëthylene (bifluorylidene), $(C_6H_4)_2C{=}C(C_6H_4)_2$, by carbon dioxide, iodine, hydrogen bromide, and ammonium sulfide (296).

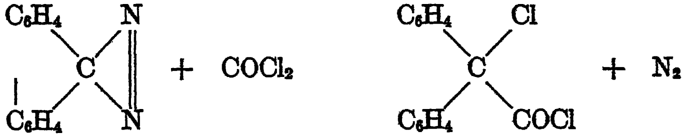
Staudinger and Gaule (294) have synthesized other derivatives from 9-diazofluorene. On standing with slightly acidified alcohol, 9-fluorenol, $(C_6H_4)_2CHOH$, was formed.



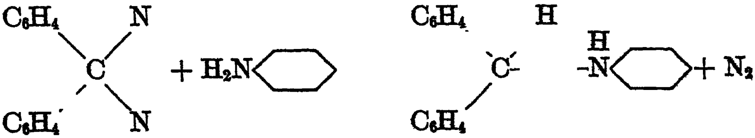
When hydrogen chloride was passed into a solution of 9-diazofluorene a good yield of 9-chlorofluorene was obtained.

9,9-Dichlorofluorene was formed when thionyl chloride was substituted for hydrogen chloride. Bromine in carbon disulfide reacted to give 9,9-dibromofluorene, and with phosgene the product was 9-chlorofluorene-9-carbonyl chloride.



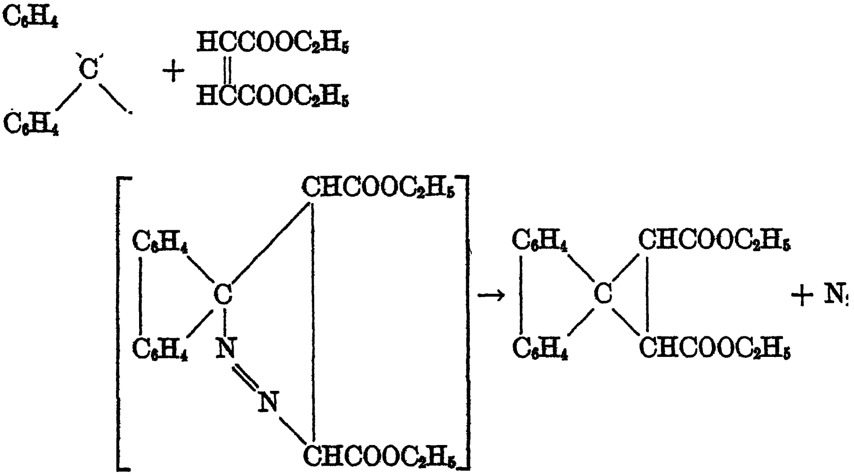


If heated with aniline, 9-fluorylphenylamine (9-fluorylaniline) resulted.



9,9-Dinitrofluorene, which decomposed on standing, was prepared by passing nitrogen dioxide into a solution of 9-diazofluorene (335, 141). These reactions are important, for they provide a ready means of synthesis of fluorene derivatives with substituents in the 9-position.

It is well known that derivatives of ethylene react with diazomethane to yield rings of three carbon atoms. Staudinger and Gaule found that 9-diazofluorene behaved similarly. Using diethyl fumarate in ether, they obtained diethyl biphenylenecyclopropane-2,3-dicarboxylate.



Ethyl cinnamate gave ethyl 1-biphenylene-2-phenylcyclopropane-3-carboxylate.

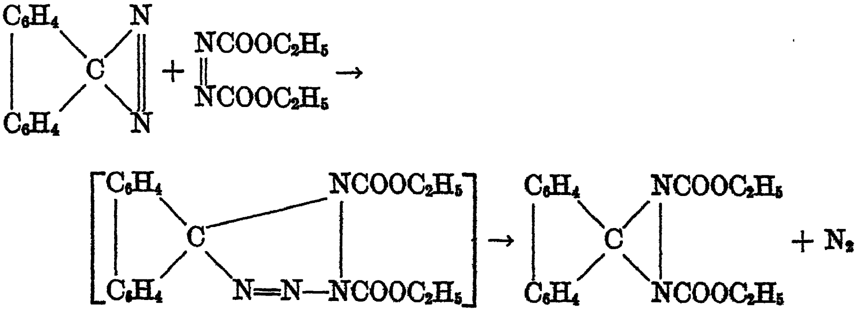
The same authors (294), having in mind this principle of ring formation, proposed an ingenious scheme for the preparation of isomeric diazo compounds and hydrazones and made attempts to carry it out experimentally. They reasoned that since ethylene derivatives gave rings with three carbon atoms, azo compounds might be expected to form rings containing one carbon and two nitrogen atoms. Compounds of the type,

$$(C_6H_4)_2C\text{—}NR\text{—}NR$$

would thus be formed with 9-diazofluorene, and by choosing R so that it could be substituted by hydrogen a hydrazi compound of the type

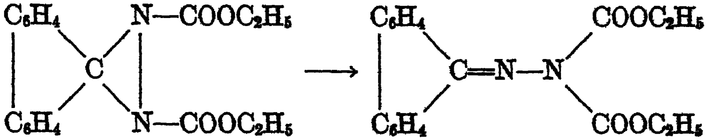
$$(C_6H_4)_2CNH\text{—}NH$$

would be obtained. This compound would be isomeric with fluorenone hydrazone, $(C_6H_4)_2C{=}N\text{—}NH_2$. The hydrazi compound on oxidation should yield a diazo compound different from 9-diazofluorene if the ordinary diazo compounds do not have the ring structure formulated by Curtius. They were successful in preparing a hydrazi compound by the following reaction.

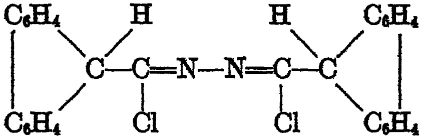


Diethyl hydrazifluorene-dicarboxylate

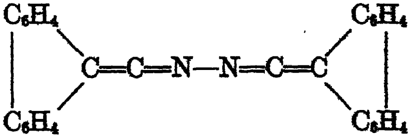
Further experiment failed, for it was found that the hydrazi compound rearranged to give diethyl fluorenone hydrazonedicarboxylate.



Stollé, Münzel, and Wolf (301) studied a series of compounds similar to those just discussed. Biphenyleneacethydrazide, $(C_6H_4)_2CHCONHNH_2$, was prepared from hydrazine hydrate and ethyl fluorene-9-carboxylate. Further treatment of this compound (biphenyleneacethydrazide) with another mole of the ester yielded *sym*-dibiphenyleneacethydrazide, $(C_6H_4)_2CHCONHNHOCHC(C_6H_4)_2$, which with phosphorus pentachloride



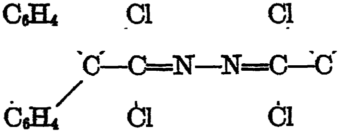
I



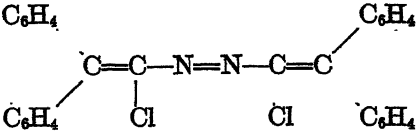
Dibiphenylenesuccinonitrile

II

gave dibiphenyleneacethydrazide chloride (I). By splitting out hydrochloric acid a compound was formed to which the unusual structure shown in formula II was assigned. It was stable and melted at 242°C. If the two hydrogen atoms in compound I attached to the 9-carbon atoms were substituted by chlorine and then removed by shaking with mercury, introduction of another double bond was attained, causing a shift of bonds in relation to the nitrogen atoms, thus:

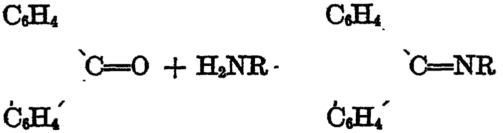

Dibiphenylenechloroacethydrazide chloride

III


Dibiphenylenechlorovinyldiimide

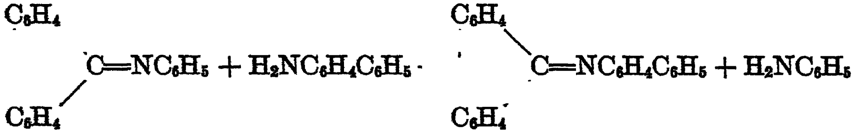
IV

Many derivatives of the type $(C_6H_4)_2C{=}NR$ have been described. Reddelien (242, cf. 230) carefully investigated the condensation of aromatic ketones with amines. Zinc chloride was found to have a catalytic effect upon the condensation.



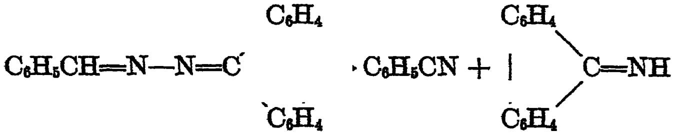
Using this method he prepared the following series of derivatives: fluorenoneanil, $(C_6H_4)_2C{=}NC_6H_5$; fluorylidene-*p*-toluidine, $(C_6H_4)_2C{=}NC_6H_4CH_3$; fluorylidene-*p*-hydroxyaniline, $(C_6H_4)_2C{=}NC_6H_4OH$; difluorylidene-*p*-diaminobenzene, $C_6H_4[N{=}C(C_6H_4)_2]_2$.

Reddelien (245) prepared other derivatives by taking advantage of displacement reactions which occur when fluorenoneanil is treated with an excess of another amine. For example, fluorenoneanil on heating with *p*-aminobiphenyl gave fluorylidene-*p*-aminobiphenyl and the theoretical amount of aniline.



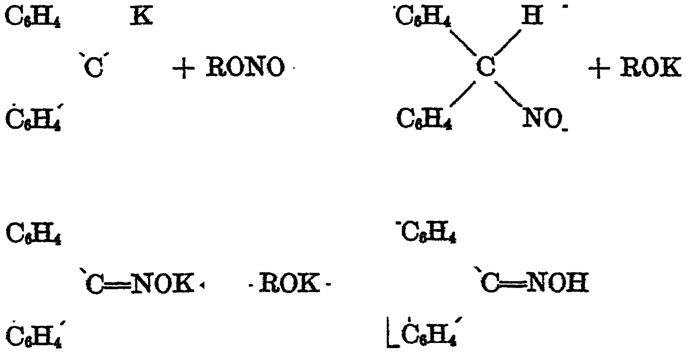
Fluorenoneanil reacted with *p*-aminobenzoic acid, methylamine, and ammonia to give fluorenoneanil-*p*-carboxylic acid, methyl-9-iminofluorene, and iminofluorene, respectively.

Iminofluorene $(C_6H_4)_2C{=}NH$ was prepared by Kliegl (163, cf. 114) by the reduction of fluorenone oxime with tin and hydrochloric acid, and it may be considered the first product of the reduction of fluorenone oxime. Pinck and Hilbert (230) prepared the imine in excellent yields from fluorenone and liquid ammonia. Boiling with water regenerated fluorenone. Iminofluorene was also formed by the thermal decomposition of benzalfluorenone ketazine (146).

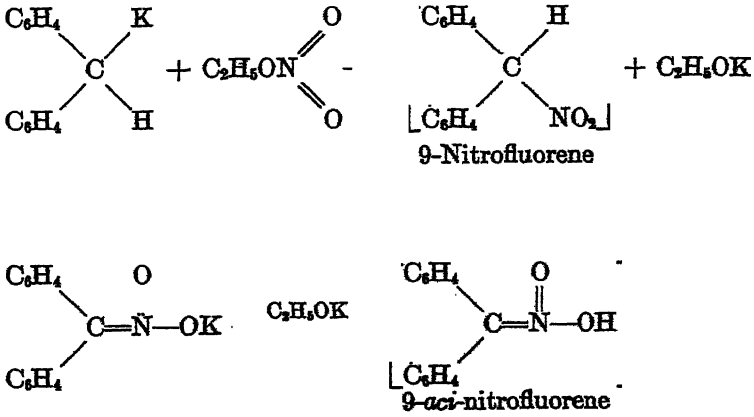


Degiorgi (68) reported the synthesis of fluorenoneaminoguanidine by the condensation of aminoguanidine and fluorenone.

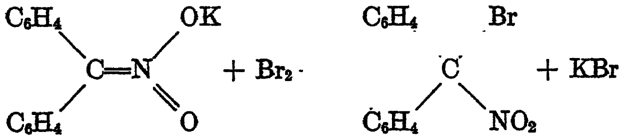
Thiele and Henle (311) in their studies of the characteristic reactions of the methylene group stated that fluorene did not react with amyl nitrite in the presence of sodium ethylate; however, when potassium ethylate was used fluorene condensed easily with alkyl nitrites to give potassium fluorenone oxime (344). The reaction probably takes place in the following manner:



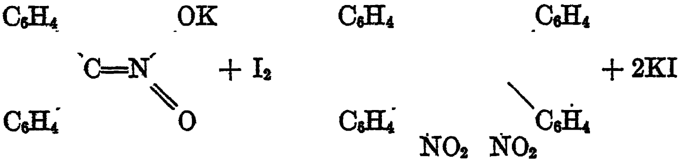
With ethyl nitrate and potassium ethylate Wislicenus and Waldmüller (344, cf. 232) obtained potassium 9-*aci*-nitrofluorene.



It gave an intense dark green color with ferric chloride. Neutralization with acid gave 9-*aci*-nitrofluorene, which in contact with ethyl alcohol was transformed into 9-nitrofluorene. Heat converted both forms into fluorenone. The potassium salt of the *aci*-form reacted with bromine to give 9-bromo-9-nitrofluorene.

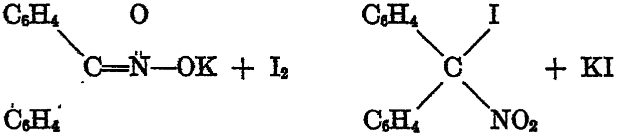


Nenitzescu (216, 217) investigated the action of iodine and other reagents upon potassium 9-*aci*-nitrofluorene. Unlike bromine and chlorine, iodine was found to cause the formation of a dimeric compound.

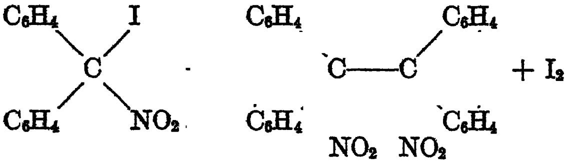


9,9′-Dinitrodifluoryl

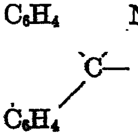
The latter compound was also obtained by the electrolysis of potassium 9-*aci*-nitrofluorene. If, however, the reaction with iodine was carried out at 0°C. the product was 9-iodo-9-nitrofluorene.



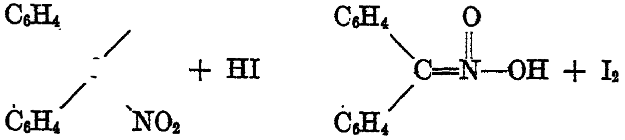
Heating 9-iodo-9-nitrofluorene for a few minutes in acetic acid also gave the dimeric dinitro compound.



The intermediate formation of the free radical, 9-nitrofluoryl, was postu-



lated. From this the mechanism of the reaction of iodine on potassium 9-*aci*-nitrofluorene was clear. Hydriodic acid reacted with 9-iodo-9-nitrofluorene to yield 9-*aci*-nitrofluorene.

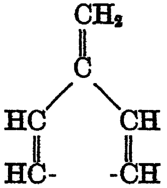


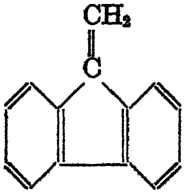
The same compound was obtained if hydriodic acid was replaced by sodium bisulfite.

The reaction between the salts of 9-*aci*-nitrofluorene and alkyl halides gave the ester, which was transformed by heat into 9-fluorenone oxime and an aldehyde.

VII. DERIVATIVES OF THE TYPE $(C_6H_4)_2C{=}C{=}$

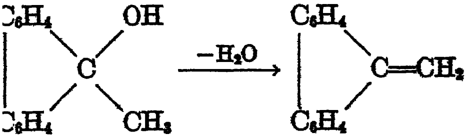
Employing Thiele's theoretical compound, fulvene (I), we may consider





II

compounds of this type as derivatives of dibenzofulvene (II). This basic compound, dibenzofulvene or 9-methylenefluorene, has been prepared, but it was quite unstable. Ferrer (95, 334) obtained it by distilling 9-methyl-9-hydroxyfluorene with aluminum phosphate *in vacuo*.



The compound was not isolated at this point, but was brominated to dibromobiphenyleneëthylene. When the dibromo compound was refluxed in alcoholic solution with zinc in daylight a polymer was obtained which may have been tribiphenylenecyclohexane. When the debromination was carried out in the dark, however, 9-methylenefluorene was obtained as crystals, melting at 53°C., which were stable for several hours.

Sieglitz and Jassoy (286, cf. 193) set out to prepare 9-methylenefluorene in the manner shown below.

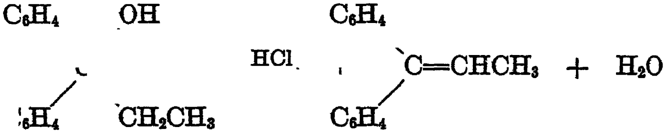
$(C_6H_4)_2CHCH_2NHCOOC_2H_5 \rightarrow$
Fluoryl-9-methylurethan

$$(C_6H_4)_2CHCH_2NH_2 \xrightarrow[\text{degradation}]{\text{Hofmann}} (C_6H_4)_2C{=}CH_2$$

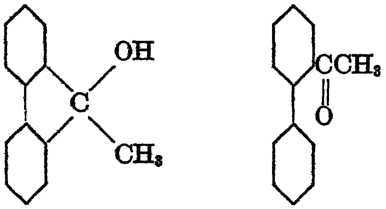
On distillation of the urethan with calcium oxide *in vacuo* and in an atmosphere of hydrogen they found to their surprise that an appreciable amount of 9-methylenefluorene was formed directly. They reported the melting point as 46–48°C. The same polymer found by Ferrer was also encountered.

$$(C_6H_4)_2CHCH_2NHCOOC_2H_5 \rightarrow (C_6H_4)_2C{=}CH_2 + C_2H_5NH_2 + CO_2$$

9-Hydroxy-9-ethylfluorene was dehydrated by means of hydrogen chloride, giving 9-ethylidenefluorene (64).

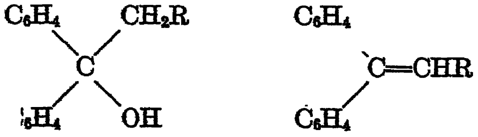


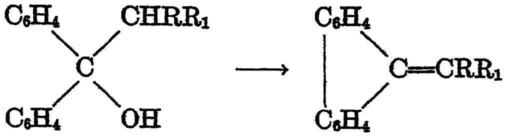
It was unstable and oxidized spontaneously in air to form an oxide which exploded at 100°C. Endeavoring to prepare 9-methylenefluorene by the same method from 9-methylfluorenol, Daufresne (64) found that rearrangement instead of dehydration took place, giving rise to an isomer of greater stability. He represented the reaction as follows:



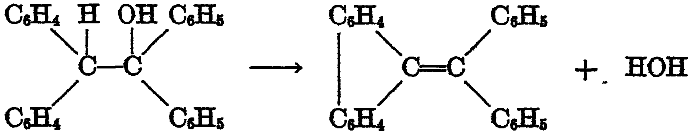
This view is probably erroneous, for he also stated that the compound did not react with hydroxylamine or semicarbazide.

The generality of this method for preparing alkyl or aromatic derivatives of 9-methylenefluorene by the dehydration of substituted fluorenols has not been investigated. The following equations represent the possibilities, where R and R_1 may be aliphatic or aromatic.

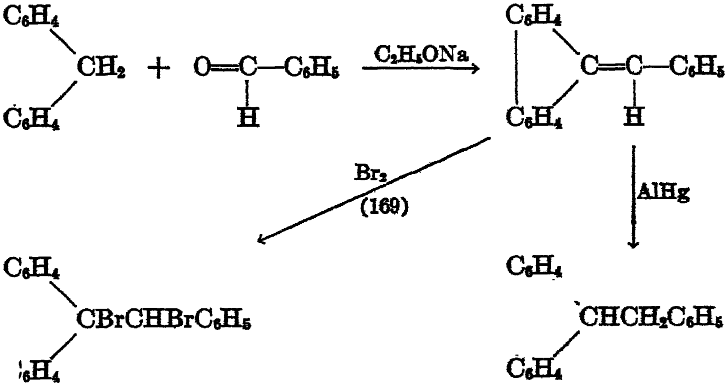




Courtot (52, 131), however, studied the dehydration of carbinols, which are isomeric with the compounds shown above, to give derivatives of 9-methylenefluorene. These compounds are of the type $(C_6H_4)_2CHC(OH)$-R_1R_2, and are prepared by the action of ketones and aldehydes on 9-fluorylmagnesium bromide. For instance, 9-fluoryldiphenylcarbinol was dehydrated quantitatively to 1,1-diphenyl-2,2-biphenyleneëthylene (158) by passing hydrogen chloride into the boiling methyl alcohol solution.



Mono-aromatic derivatives, of the type $(C_6H_4)_2C{=}CHR$, have been more easily obtained by the condensation of aromatic aldehydes with fluorene, using sodium methylate or ethylate as the condensing agent (311). Bromine added normally to these compounds to give the dibromo derivatives. Reduction of the double bond was effected with aluminum amalgam. Thiele and Henle (309, 311) prepared numerous compounds in this way. For example, 9-benzylidenefluorene was prepared from benzaldehyde and fluorene. The condensation, bromination, and reduction are shown in the following equations.



Furfural, cinnamaldehyde, and anisaldehyde reacted similarly. Sieglitz (282) extended the series, using more complex aldehydes, and investigated the characteristic halochromism of the compounds in concentrated sulfuric acid. Table 5 summarizes his results. It is interesting to note the distinct change of halochromism encountered with the isomeric chlorobenzaldehydes.

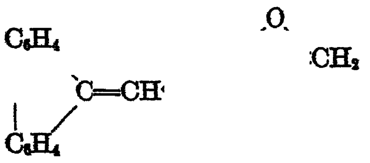
DeFazi (66) carried out this condensation with piperonal (3,4-methylenedioxybenzaldehyde) and 4-dimethylaminobenzaldehyde. Together with the expected 3,4-methylenedioxybenzylidenefluorene and 4-dimethylaminobenzylidenefluorene he obtained more deeply colored compounds which he assumed to be isomers. Bergmann (24) encountered similar deeply colored compounds on condensing benzaldehyde, *p*-methoxybenzaldehyde, and α-naphthaldehyde with fluorene and proved them to be the vinylene homologs. Reasoning by analogy Bergmann (24) thought it likely that DeFazi's compounds embodied a similar relationship. He proved by synthesis that this was the case. DeFazi's two compounds from piperonal were then 3,4-methylenedioxybenzylidenefluorene (I) and 3,4-methylenedioxycinnamylidenefluorene (II). The formation of II is probably due to the intermediate production of acetaldehyde from sodium ethylate (236, 258).

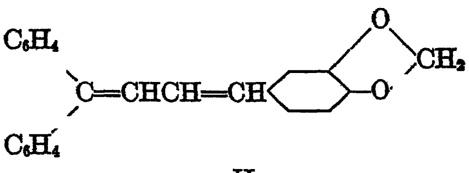
TABLE 5

Halochromism in concentrated sulfuric acid

COMPOUND	COLOR	MELTING POINT °C.	HALOCHROMISM
9,9′-Isophthalaldifluorene	Yellow	178–179	Deep green
9,9′-Terephthalaldifluorene	Yellow	209–210	Olive-green
9-*p*-Bromobenzylidenefluorene	Yellow	144	Green blue
9-*m*-Bromobenzylidenefluorene	Yellow	92–93	Deep green
9-*m*-Iodobenzylidenefluorene	Yellow	103	Deep green
9-*o*-Chlorobenzylidenefluorene*	Yellow	176	Dark brown
9-*m*-Chlorobenzylidenefluorene	Light yellow	90.5	Deep green
9-*p*-Chlorobenzylidenefluorene	Faint yellow	149.5	Deep blue

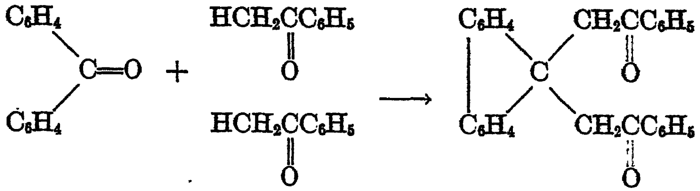
* Only obtained in a 15 per cent yield.



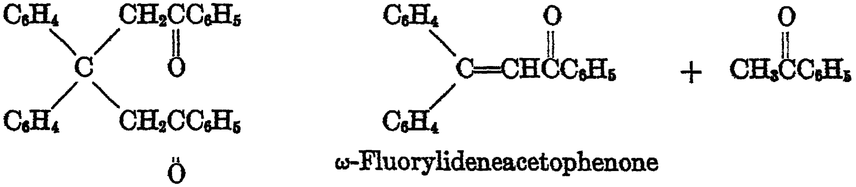


II

Dufraisse and Carvalho (76) condensed fluorenone and acetophenone in ether, using sodamide as the condensing agent, to obtain 9,9-diphenacylfluorene.

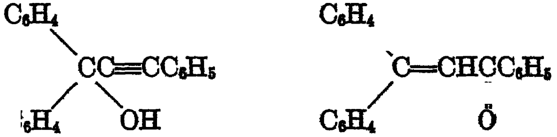


On pyrolysis at 230°C. 9,9-diphenacylfluorene decomposed into ω-fluorylideneacetophenone (299) and acetophenone.

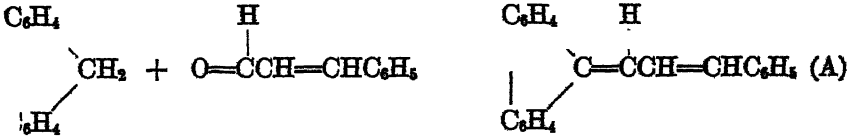


ω-Fluorylideneacetophenone

ω-Fluorylideneacetophenone was also prepared using hydrogen chloride instead of sodamide. These same authors, in attempts to prepare rubene derivatives of fluorene, synthesized phenylethynylfluorenol from fluorenone and phenylacetylene (77). Isomerization took place readily giving the same ω-fluorylideneacetophenone.



Kuhn and Winterstein (182) prepared a series of biphenylene analogs by condensing fluorene and appropriate aldehydes, as shown in the following equations:



1-Biphenylene-4-phenylbutadiene-1,3[8]

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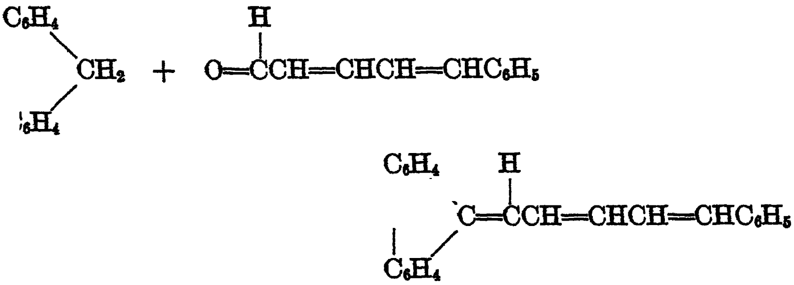
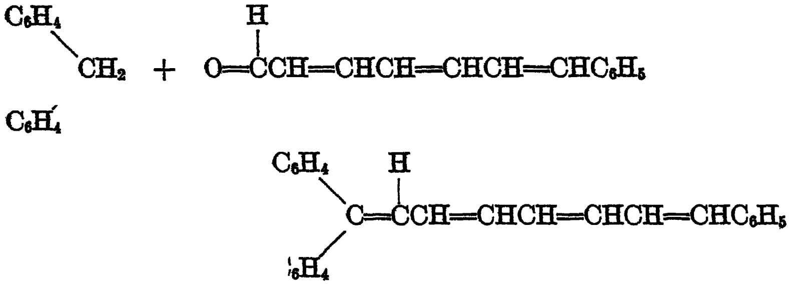
[8] On reduction with aluminum amalgam this compound gave 9-fluoryl-1-benzyl-2-ethylene; with sodium amalgam, 1-biphenylene-4-phenylbutene; and catalytically with hydrogen, 9-fluoryl-1-phenyl-3-propane.



(B)

1-Biphenylene-6-phenylhexatriene-1,3,5

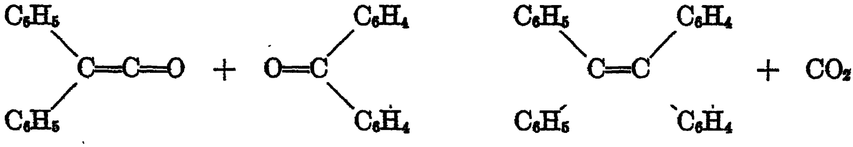


(C)

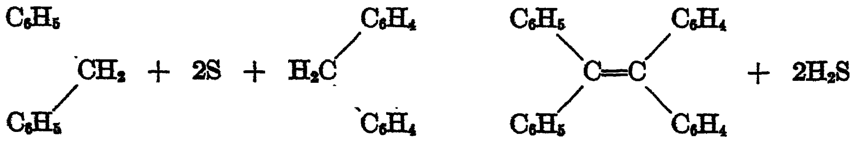
1-Biphenylene-8-phenyloctatetraene-1,3,5,7

The yield in reaction A was 63 per cent, but in reactions B and C it dropped to 11 per cent and 5 per cent, respectively.

Two novel reactions led to the production of 1,1-diphenyl-2,2-biphenyleneëthylene (see page 313). Staudinger and Gaule (293) obtained it from diphenylketene and fluorenone.

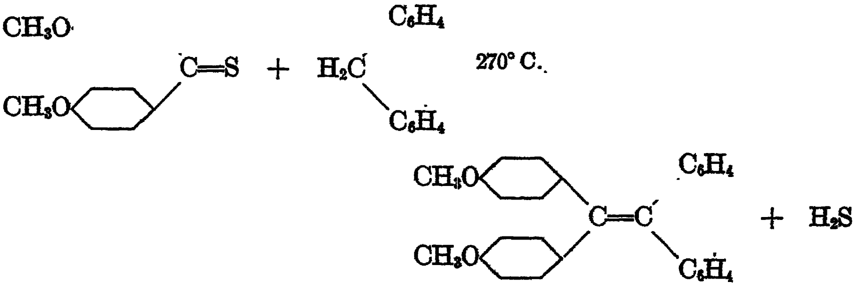


Szperl and Wierusj (307) reported it as the main product when a mixture of diphenylmethane and fluorene was heated with sulfur until hydrogen sulfide ceased to be evolved.



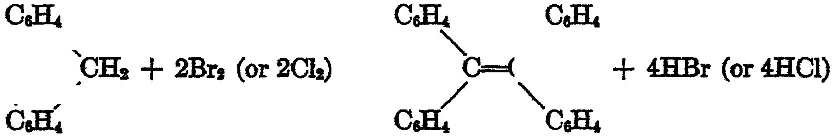
It crystallized from acetone in needles containing one molecule of acetone of crystallization, which it lost on exposure to air. The by-products of the reaction were the dimers, both saturated and unsaturated, of fluorene and diphenylmethane.

Schönberg (274) refined the method of Szperl by using a thiobenzophenone instead of free sulfur.

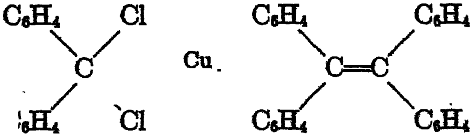


p,p′-Dimethoxydiphenyl-9-methylenefluorene

The unsaturated dimolecular compound of fluorene, dibiphenylene-ethylene or bifluorylidene, $(C_6H_4)_2C{=}C(C_6H_4)_2$, is formed with ease, owing to the reactivity of the hydrogen atoms in the 9-position. De la Harpe and van Dorpe (70) first described its preparation. Mantz (192) found that the action of chlorine or bromine at high temperatures resulted in its formation.



Schmidt and Wagner (271, cf. 289) obtained it in very good yields by treating 9,9-dichlorofluorene with copper powder in benzene solution.



Bifluorylidene is one of the few colored hydrocarbons; it is deep red and melts at 187–188°C. (cf. page 296).

VIII. DERIVATIVES OF THE TYPE $(C_6H_4)_2C<$

Derivatives of fluorene in which either one or both of the hydrogen atoms of the 9-carbon atom are replaced by various substituents are well known.

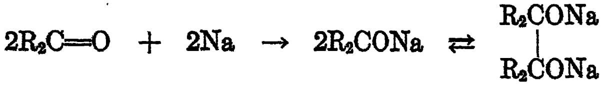
A. Hydroxy compounds. 9-Fluorenols

The reduction of fluorenone to fluorenol (9-hydroxyfluorene) and to the corresponding pinacol has been studied in some detail. 9-Fluorenol was first obtained by Barbier (14) from fluorenone, using sodium amalgam in alcoholic solution. Werner and Grob (332) used zinc dust and potassium hydroxide and zinc dust and ammonia. Aluminum amalgam in alcohol

$$(C_6H_4)_2CO \xrightarrow{[H]} (C_6H_4)_2CHOH$$

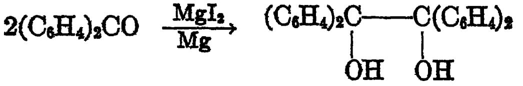
seems to be the most satisfactory reducing agent, giving a quantitative yield (47).

Bachmann (9) reported that when the reduction was carried out in ether solution with the theoretical amount of sodium, fluorenopinacol was obtained in a 95 per cent yield after hydrolysis with dilute acid. An excess of sodium seemed to favor the formation of fluorenol, for with a 30 per cent excess of sodium, 75 per cent of the pinacol and 25 per cent of fluorenol was formed. It is evident from his work that "the sodium derivatives of ketones, the so-called metal ketyls, are not, therefore, monomolecular free radicals but sodium pinacolates or equilibrium mixtures of sodium-ketyl and sodium pinacolate in which the equilibrium is nearly entirely in favor of the sodium pinacolate."



$$2R_2C{=}O + 2Na \rightarrow 2R_2CONa \rightleftarrows \begin{array}{c} R_2CONa \\ | \\ R_2CONa \end{array}$$

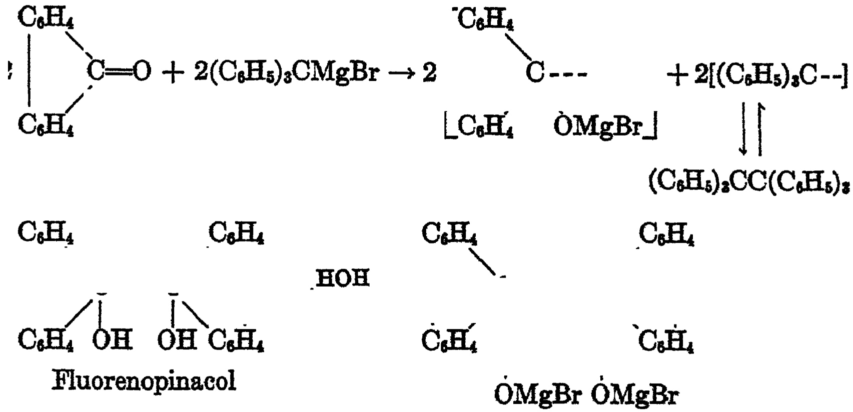
Gomberg and Bachmann (121), in their experiments with the reducing action of mixtures of magnesium iodide (or bromide) and magnesium on aromatic ketones, also obtained the pinacol, this time in a 99 per cent yield.



$$2(C_6H_4)_2CO \xrightarrow[Mg]{MgI_2} \begin{array}{cc} (C_6H_4)_2C & \text{---}C(C_6H_4)_2 \\ | & | \\ OH & OH \end{array}$$

It is important to note that fluorenone, fluorenol, and fluorenopinacol tended to form very definite complexes with each other. Gomberg and Bachmann obtained a tan-colored complex, m.p. 123–124°C., consisting of 1 mole of fluorenopinacol and 1 mole of fluorenone. Bachmann found another complex of fluorenol and fluorenopinacol, m.p. 151°C. It was crystalline and the proportions were equimolar.

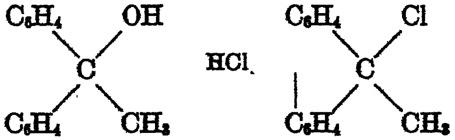
Bachmann (8) also carried out the reduction of fluorenone with triphenylmethylmagnesium bromide.



The presence of the free radicals was postulated on the basis of definite color changes which the solution underwent during the reaction. The yield of the pinacol was 80 per cent.

Meerwein (196) prepared the methyl and ethyl analogs and rearranged them to the pinacolones, 9,9-methylacetylfluorene, etc. The reduction of fluorenone with zinc and acetyl chloride gave a pinacolone, 9,9-biphenylenephenanthrone, directly (28, 121, 129, 163, 168). It may also be prepared in the usual way.

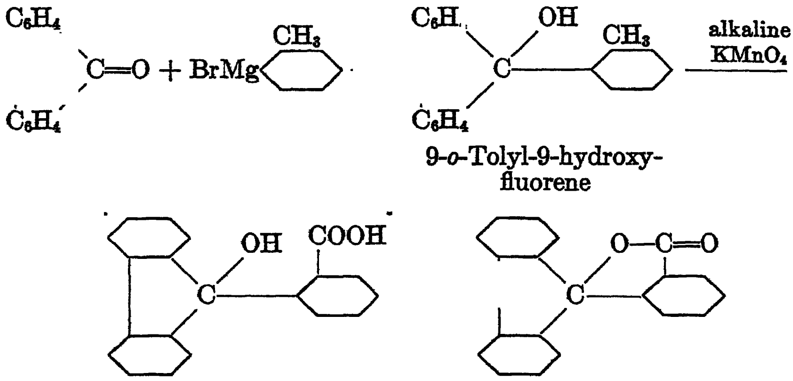
Fluorenone reacts normally with Grignard reagents and constitutes the principal method of preparing substituted fluorenols (cf. page 333). Methylmagnesium iodide (or bromide) and fluorenone gave 9-methyl-9-fluorenol (95, 333, 334). The substituted fluorenols on treatment with halogen acids were converted easily to the halogen compound; thus, methylfluorenol in ether with hydrogen chloride yielded 9-methyl-9-chlorofluorene (compare Daufresne (64)).



More complex fluorenols have been synthesized by the same method. Ullmann and von Wurstemberger (317) prepared 9-phenylfluorenol from phenylmagnesium bromide and fluorenone. Schniepp and Marvel (273) extended this particular type of synthesis by employing *p*-alkylphenylmagnesium halides. The following were synthesized: 9-*p*-ethylphenylfluorenol, 9-*p*-*n*-propylphenylfluorenol, and 9-*p*-tolylfluorenol (cf. 176). The chloro compounds were prepared by treating the crude fluorenols with hydrochloric acid and calcium chloride. The chlorine atom was especially reactive, as evidenced by the formation of alkyl ethers by merely heating with the proper alcohol. The chloro compounds on heating in benzene with copper bronze in an atmosphere of hydrogen gave the corresponding di-*p*-alkylphenyldibiphenyleneëthanes.

Bergmann and Schuchardt (28) similarly prepared 9-*p*-anisylfluorenol and 9-*p*-anisyl-9-chlorofluorene (cf. 323).

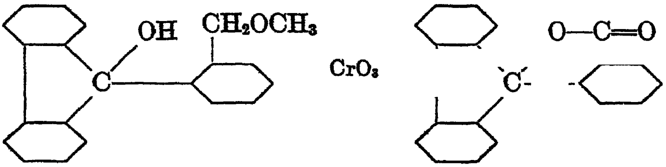
Weiss and Knapp (329) prepared a 9-substituted fluorenol which was eventually transformed into a lactone.



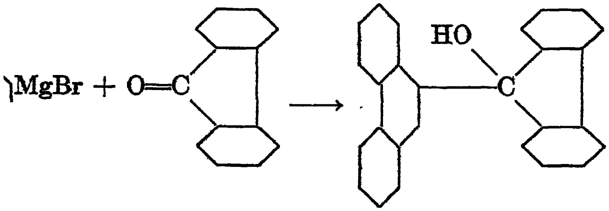
9-*o*-Tolyl-9-hydroxy-fluorene

o-Biphenylenephthalide

Koelsch (171) obtained the same *o*-biphenylenephthalide by the oxidation of 9-(*o*-α-ethoxytolyl)fluorenol, prepared from *o*-(α-ethoxytolyl)magnesium bromide and fluorenone.

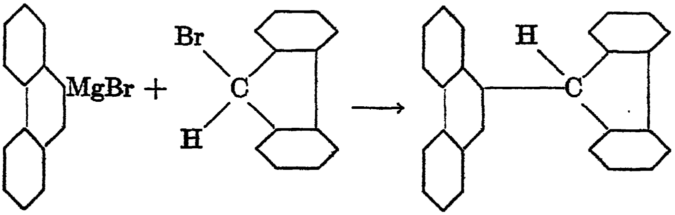


A fluorenol in which the phenanthrene nucleus is substituted in the 9-position has been prepared by Bachmann (10). This fluorenol on reduc-



9-(9′-Phenanthryl)fluorenol

tion with hydriodic acid[9] gave a quantitative yield of 9-(9′-phenanthryl)-fluorene, which was also prepared by the modified Grignard synthesis shown below.



9-(9′-Phenanthryl)fluorene

There are numerous other examples of synthesis from fluorenone and Grignard reagents (51, 130), and in all cases the reaction seems to go quite well.

Schmidt and Mezger (265) reported the existence of 9,9-dihydroxyfluorene, m.p. 94°C. It resulted from the hydrolysis of the so-called α-form of 9-acetoxyfluorene (9-fluoryl acetate) which melted at 69–70°C. The β-form of this compound was said to melt at 208–209°C., but it was obtained in such small amounts that its hydrolysis could not be investigated. It is probable that the two compounds were $(C_6H_4)_2CHOCOCH_3$ and $(C_6H_4)_2C(OH)COCH_3$ and not stereoisomeric forms.

No confirmation of the existence of 9,9-dihydroxyfluorene has ever been made. Reactions that might be expected to give the dihydroxy compound produce fluorenone (289).

B. Halogen compounds

9-Chloro-, 9,9-dichloro-, 9-bromo-, and 9,9-dibromo-fluorene (see pages 305–320) have been prepared. Two iodine derivatives, 9-iodofluorene (181, 321) and 9-iodo-9-nitrofluorene (see page 311), are also known. It is probable that other iodo derivatives could be prepared under anhydrous conditions (238).

9-Chlorofluorene is reported to be best prepared by the action of phosphorus pentachloride on fluorenol (57, 163, 166, 294, 332). Thionyl chloride also was found to be a very efficient reagent for the preparation of 9-chlorofluorene from the fluorenol (153).

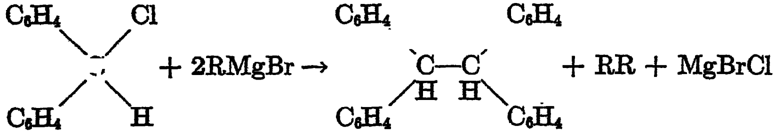
Probably the treatment of fluorenol in acetic acid solution with dry hydrogen chloride, with or without zinc chloride, is equally effective (57).

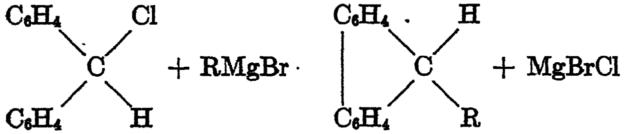
9,9-Dichlorofluorene was first prepared by Ida Smedley (289) by the action of phosphorus pentachloride on fluorenone. It formed large color-

[9] Hydriodic acid is one of the best reducing agents for accomplishing the transition from fluorenols to fluorenes. See Vanscheidt (J. Russ. Phys. Chem. Soc. 58, 139 (1926); Chem. Abstracts 21, 581 (1927)).

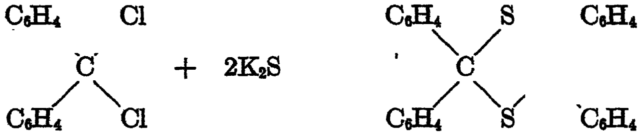
less prisms melting at 103°C. Schmidt and Wagner (271, cf. 294) gave the melting point as 99°C. The dichloride proved to be a very reactive substance. Warming with hydroxylamine or phenylhydrazine gave fluorenone oxime and fluorenone phenylhydrazone, respectively. Treatment with alcoholic potassium hydroxide yielded 9,9-diethoxyfluorene; with phenol 9,9-diphenoxyfluorene was obtained.

Miller and Bachman (199) investigated the value of 9-chlorofluorene for synthetic purposes. It was found to undergo two types of reactions with alkyl magnesium halides.


(I)

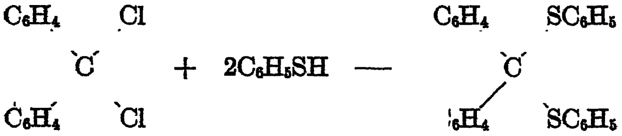

(II)

Several sulfur compounds of fluorene have been prepared from fluorenone dichloride. Ida Smedley (289) prepared thiofluorenone from potassium sulfide and the dichloride. It was an intense red in color. Bergman and



Hervey maintained that Smedley's compound was a disulfide (26).

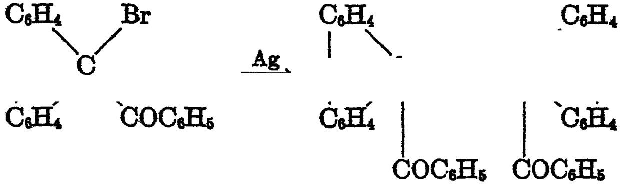
On heating phenyl mercaptan for a long period with 9,9-dichlorofluorene in benzene solution 9,9-diphenylmercaptofluorene was formed. Other reactions of this type have also been studied (25, 30, 191, 197, 275, 276, 277, 278).



9-Bromofluorene has been prepared in good yields by the action of hydrogen bromide on fluorenol (2, 154, 292).

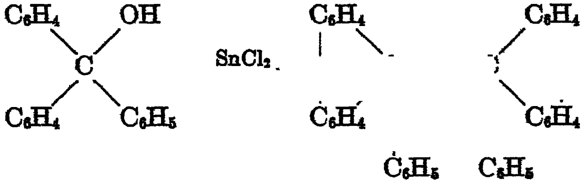
Fluorene derivatives in which one of the hydrogen atoms on the 9-carbon atom is replaced by an alkyl or aromatic radical and the other hydrogen atom by chlorine or bromine may be synthesized easily by the action of the Grignard reagent on fluorenone followed by treatment with the phosphorus or hydrogen halide (231, 259). Hydriodic acid reduces the hydroxyl group and $(C_6H_4)_2CHR$ is obtained.

These halogen compounds serve as the starting point for the synthesis of symmetrically substituted ethanes involving the fluorene molecule (see page 320). The ethanes are very easily oxidized, usually on exposure to air, to give peroxides. Several cases of the formation of free radicals have added to the interest of these compounds. For example, 9-bromo-9-benzoylfluorene on treatment with silver powder gave dibenzoylbifluoryl.



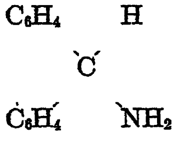
The hot colored solutions of this compound did not obey Beer's law. This led to the assumption of the presence of the free radical, benzoylfluoryl (115).

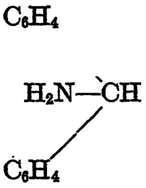
Compounds of the type $[(C_6H_4)_2ArC—]_2$ have been prepared by Gomberg and Cone (122) and have been shown by Schlenk, Herzenstein, and Weickel (260) to form free radicals. Schniepp and Marvel (273) investigated di-*p*-alkylphenylbiphenyleneëthanes and the effect of the *p*-alkyl group on the dissociation of the ethane (cf. 122, 259, 260). All the compounds readily formed peroxides. The reduction of 9-substituted fluorenols with stannous chloride constitutes another method of preparing these dimolecular compounds. For example, on boiling an acetic acid solution of 9-phenylfluorenol for 15 min. with stannous chloride a good yield of 1,1-diphenyl-2,2-dibiphenyleneëthane was obtained (323).



C. 9-Aminofluorene and derivatives

The intensive investigation of 9-aminofluorene was largely due to the isomerism attributed to it by Schmidt and Stützel (270). Previously Wegerhoff (328) had reported that it melted between 50° and 60°C. Kerp (159) gave a melting point of 161°C., but the compound melting at this temperature was shown by Kuhn and Jacob (180) to be the acetate. Schmidt and Stützel prepared the amine by reduction of fluorenone oxime with zinc and acetic acid. They reported that the principal product was the α-form, which melted at 53–55°C. A β-form, which melted at 123°C., was also isolated. The latter form was converted into the α-form by boiling in solvents. The two modifications, however, yielded identical derivatives, with the exception of the phenylcarbamide derivative. They prepared the symmetrical thiourea, the hydrochloride, and the acetyl compound. Schmidt and Stützel supposed this to be a case of *cis–trans* isomerism. This would, however, require a folded ring type of stereoisomerism (see section XVIII).

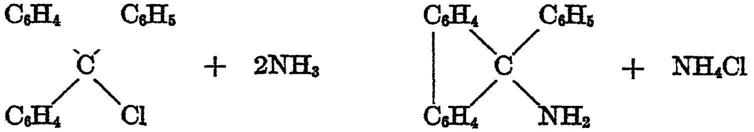


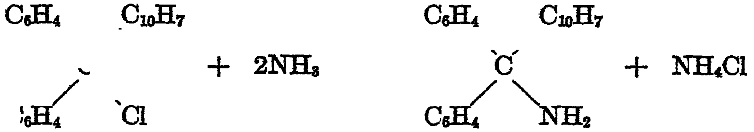


Kuhn and Jacob (179), in their reinvestigation of the reduction, claimed to have isolated the α-form but not the β-form; however, they reported a γ-form that melted at 64°C. Kliegl, Wünsch, and Weigele (165) stated emphatically that only one 9-aminofluorene exists. Ingold and Wilson (155) have recently improved the preparation of 9-aminofluorene from fluorenone oxime by reduction with zinc. 9-Aminofluorene, by this method, was obtained as needles from ligroin, melting at 62–63°C. We have carried out this preparation several times with excellent results, and think that no doubt most of the conflicting results in the investigation of this compound have been due to its relative instability in air and its tendency to absorb carbon dioxide. It is probable that the β-form was the carbonate.

Ingold and Wilson (155) have shown that 9-aminofluorene reacts with ketones in the usual way to give Schiff bases. Using acetophenone and fluorenone as ketones, they obtained α-phenylethylidene-9-aminofluorene, $(C_6H_4)_2CHN{=}C(CH_3)C_6H_5$, and fluorylidene-9-aminofluorene, $(C_6H_4)_2CHN{=}C(C_6H_4)_2$.

The reactivity of fluorenes with halogen substituted in the 9-position would lead us to expect an easy preparation of 9-aminofluorene by treatment with anhydrous ammonia. Courtot and Peticolas (56), using 9-chlorofluorene and liquid ammonia, obtained only traces of the primary amine, together with the secondary amine and dibiphenyleneëthylene. It seems to us that this reaction is influenced by the labile nature of the hydrogen in the 9-position, because when this hydrogen was replaced by a relatively large group, such as phenyl or naphthyl, the compound reacted normally with ammonia to give the 9-substituted primary amine. Thus Pinck and Hilbert (231) readily prepared 9-phenyl-9-aminofluorene and 9-α-naphthyl-9-aminofluorene by this reaction. The secondary amine could be



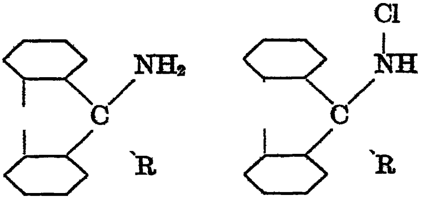


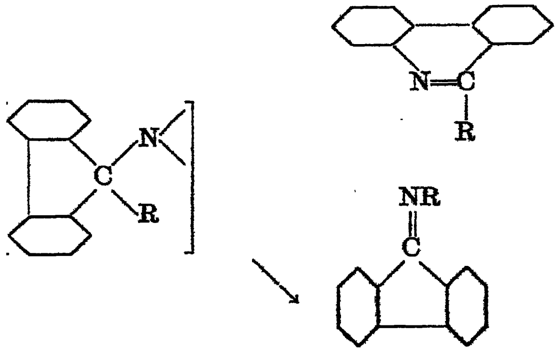
formed by using an excess of ammonia in a steel bomb at 180°C. A result similar to Courtot's was experienced in attempting to prepare 9-methyl-9-aminofluorene from 9-methyl-9-bromofluorene and ammonia. Dibiphenyleneëthylene, the secondary amine, and the primary amine were the products of the reaction.

The character of the group attached to nitrogen also seems to have an important effect upon the course of the reaction. If aromatic or aliphatic primary amines were used the reaction took place smoothly. Courtot and Peticolas (cf. 242 and 154) in this way prepared *N*-phenyl-9-aminofluorene (fluorylaniline), *N*-*p*-tolyl-9-aminofluorene, and *N*-α-naphthyl-9-aminofluorene. (Cf. page 304 for di-9-fluorylamine $[(C_6H_4)_2CH]_2NH$.)

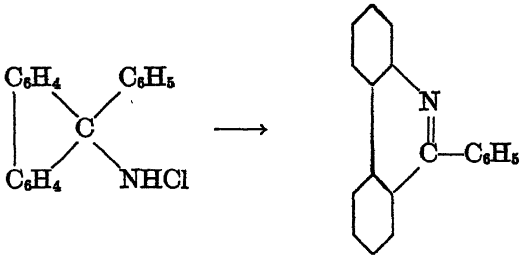
Compounds of the type $(C_6H_4)_2CHNHR$ may also be prepared by the reduction of *N*-substituted ketimines of fluorenone.

Recently Pinck and Hilbert (231) have published the results of an investigation into the application of the Stieglitz rearrangement (233). In an *N*-substituted 9-aminofluorene, stabilization can be attained by undergoing two types of rearrangement.

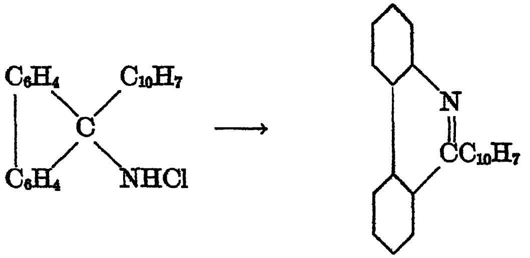




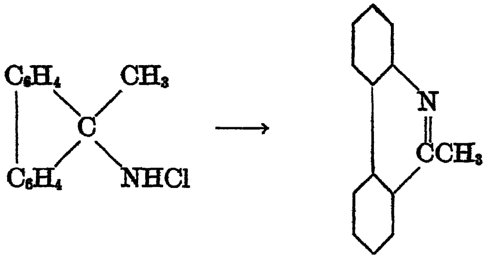
Two products are then theoretically possible, either a phenanthridine derivative or an imine. Pinck and Hilbert reasoned that the strained condition of the cyclopentadiene ring should favor the opening of the ring with subsequent reformation to give the phenanthridine type. This was found to be true. The monochloroamines[10] of 9-phenyl-9-aminofluorene, 9-α-naphthyl-9-aminofluorene, and 9-methyl-9-aminofluorene were prepared by treating alcoholic solutions of the amines with hypochlorous acid. Their rearrangement was accomplished in an anhydrous pyridine[11] solution of the chloroamine with excess dry sodium methylate.



9-Phenylphenanthridine



9-α-Naphthylphenanthridine



9-Methylphenanthridine

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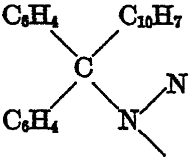
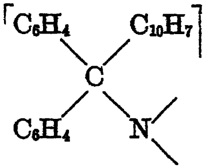
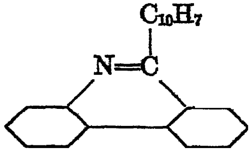
[10] The dichloroamine was obtained by passing an excess of chlorine into an alcoholic solution of 9-phenyl-9-aminofluorene. It is remarkably stable.

[11] The purpose of the pyridine was to catalyze the removal of hydrogen chloride. Color changes during the reaction indicated an intermediate compound, possibly of the free radical type.

Similarly 9-α-naphthylphenanthridine was also prepared by the thermal decomposition of 9-α-naphthyl-9-fluoreneazide (231).







In none of these reactions was any imino derivative formed. It was concluded that the strained condition of the five-membered ring instead of the relative electronegativeness of the substituents of the tertiary carbon atom was probably the factor controlling the rearrangement of the intermediate compound.

In 1930 Nakamura (214) reported that the hydrochloride of 9-aminofluorene showed a very definite local anesthetic action when applied to the tongue. The hydrochlorides of the three amino compounds prepared by Pinck and Hilbert (231) also possess this property. We have confirmed Nakamura's experience with 9-aminofluorene. We have also prepared 2-benzoyl-9-aminofluorene and find that although the local anesthetic action of its hydrochloride is slower to take effect it is more intense and prolonged.

D. *Fluorene-9-carboxylic acids*

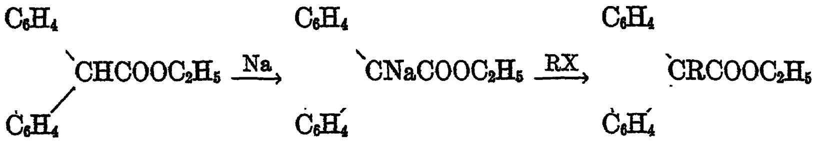
Fluorene-9-carboxylic acid (biphenyleneacetic acid) has been obtained in a variety of ways (50, 69, 109, 324, 325). Several of the indirect methods have already been described. The most direct method of preparation is, of course, the reaction between 9-sodium fluorene and carbon dioxide. Schlenk and Bergmann (257) prepared the sodium compound by treating fluorene with the sodium derivative of triphenylmethane. These authors reported two forms of the acid, the α-form melting at 222°C. and the β-form melting at 232°C. Kliegl (164) repeated the work and obtained only one compound which melted at 221–223°C. with slight evolution of gas. Characteristic derivatives have been prepared by Stollé and Wolf (302) and Wislicenus and Ruthing (343). Fluorene-9-carbonyl chloride was obtained from the acid by the action of thionyl chloride.[12] It formed unstable crystals which were hydrolyzed by water with extraordinary ease.

---

[12] If 2 parts of thionyl chloride are used, dibiphenylenesuccinyl dichloride, $(C_6H_4)_2C(COCl)C(COCl)(C_6H_4)_2$, is formed. Further heating (200 hr.) with an excess of thionyl chloride gives 9-chlorofluorene-9-carbonyl chloride, $(C_6H_4)_2Cl(COCl)$.

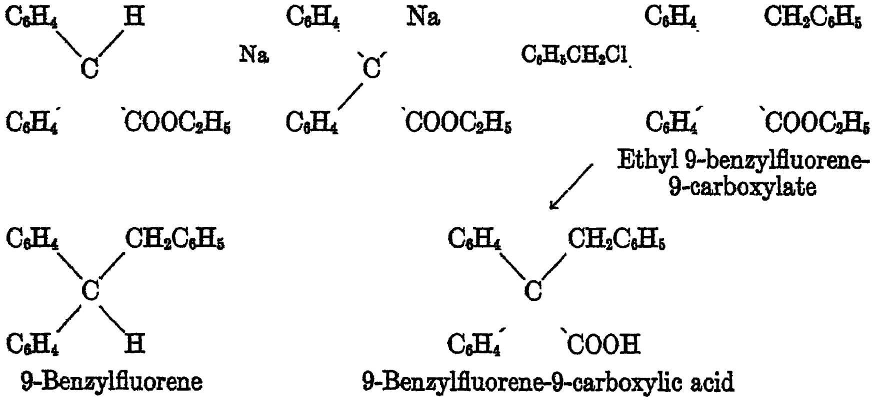
The anilide was formed from either the chloride or the ethyl ester by action with aniline at 150°C.; it was a white crystalline powder, melting at 255°C. The amide, $(C_6H_4)_2CHCONH_2$, prepared from the chloride and ammonia, crystallized in needles, melting at 251°C. Adickes (2) reported the preparation of the ethyl ester in 90 per cent yields.

Wislicenus and Mocker (340, cf. 292) found that ethyl fluorene-9-carboxylate itself formed a sodium or potassium derivative which reacted easily with organic halides. The metal derivative was very sensitive to



$$(C_6H_4)_2CHCOOC_2H_5 \xrightarrow{Na} (C_6H_4)_2CNaCOOC_2H_5 \xrightarrow{RX} (C_6H_4)_2CRCOOC_2H_5$$

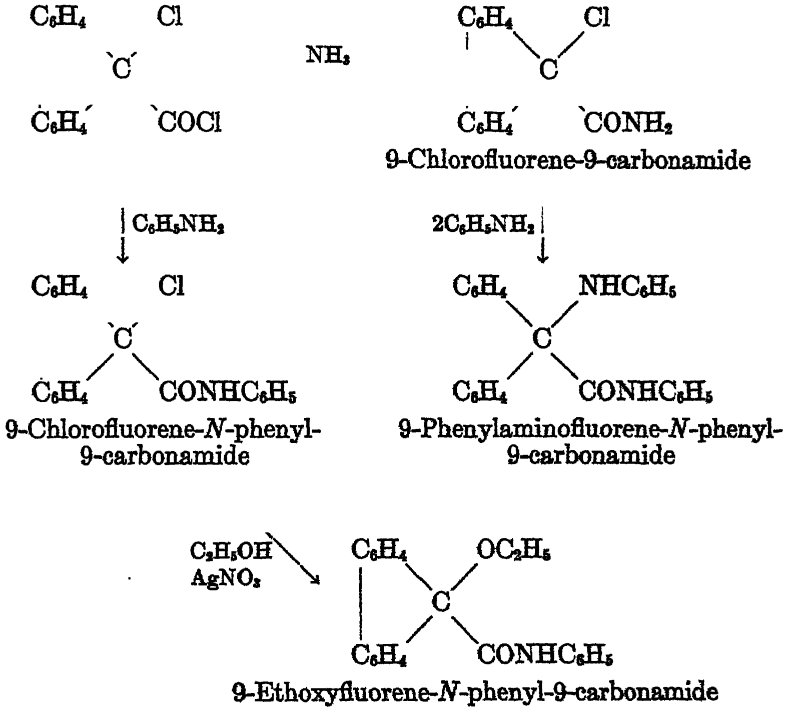
atmospheric oxygen and the reaction was carried out in an atmosphere of hydrogen. The substituted esters were saponified by boiling with potassium hydroxide, but care was needed, since carbon dioxide was split out on long boiling. The free acids, $(C_6H_4)_2CRCOOH$, also lost carbon dioxide on heating to about 250°C. Since all these reactions proceed smoothly and fluorene-9-carboxylic acid is easily obtained, this method constitutes a very convenient one for the synthesis of 9-substituted derivatives of fluorene. For example, 9-benzylfluorene was synthesized in the following way:


Na
$C_6H_5CH_2Cl$
Ethyl 9-benzylfluorene-9-carboxylate
9-Benzylfluorene
9-Benzylfluorene-9-carboxylic acid

Wislicenus and Mocker (340) prepared a number of similar derivatives, as did Ruhemann (248).

Perhaps the best known 9-derivative of fluorene-9-carboxylic acid is 9-hydroxyfluorene-9-carboxylic acid, $(C_6H_4)_2C(OH)COOH$, usually called biphenyleneglycolic acid. As stated before, it is easily obtained from phenanthraquinone by heating with aqueous alkali. Klinger (166) prepared it in 94 per cent yields by heating 1 part of phenanthraquinone with 10 parts of 20 per cent sodium hydroxide for 3 hr. at 70–80°C. The esters were prepared by the use of hydrogen chloride with the proper alcohol. The hydroxyl radical was easily replaced, for even a small excess of hyrogen chloride in the esterification gave rise to the 9-chloroester. The methyl hydroxy ester melts at 159°C. and the ethyl ester at 92°C. (109).

Phosphorus pentachloride reacted with biphenyleneglycolic acid to give 9-chlorofluorene-9-carbonyl chloride, $(C_6H_4)_2CClCOCl$, in good yields. Klinger (166, 167) prepared several derivatives of this compound, as shown below.



9-Chlorofluorene-9-carbonamide

9-Chlorofluorene-*N*-phenyl-9-carbonamide

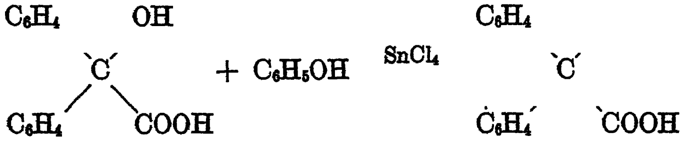
9-Phenylaminofluorene-*N*-phenyl-9-carbonamide

9-Ethoxyfluorene-*N*-phenyl-9-carbonamide

The analogous bromine compound (9-bromofluorene-9-carbonyl bromide) was prepared by heating biphenyleneglycolic acid with phosphorus tribromide; it reacted similarly to the chloro compound.

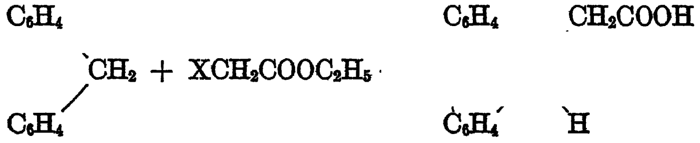
Bistrzycki and von Weber (31) studied the condensation of phenols and phenyl ethers with biphenyleneglycolic acid, using concentrated sulfuric acid or stannic chloride as the condensing agent. For example, 9-*p*-

hydroxyphenylfluorene-9-carboxylic acid was prepared by boiling biphenyleneglycolic acid and phenol in benzene solution containing some



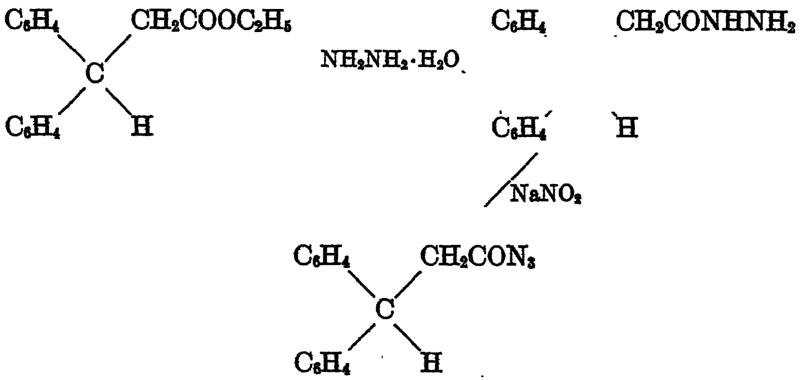
stannic chloride. Some of the *o*-hydroxylactone was also formed, showing that condensation took place to a small extent in the ortho position. On heating or boiling in aqueous sodium carbonate solution this and other similar compounds lost carbon dioxide to give 9-fluorene derivatives.

Fluorene-9-acetic acid, $(C_6H_4)_2CHCH_2COOH$, is closely related to 9-hydroxyfluorene-9-carboxylic acid and may be considered here. It was most simply prepared by heating a monohalogenoacetic ester with fluorene at a relatively high temperature in the presence of alkali (347).



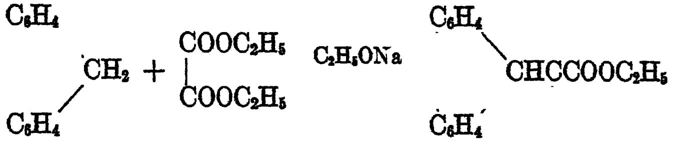
Other methods have also been reported (193, 339, 340). Zimmerman and Wilcoxon (349), in their recent experiments on the effect of various compounds upon the growth of plants, found that fluorene-9-acetic acid had some effect in producing root initiation.

Sieglitz and Jassoy (285) prepared fluorene-9-acethydrazide by boiling ethyl fluorene-9-acetate with hydrazine hydrate. The acid azide was obtained in quantitative yields by treating the hydrazide in acetic acid with sodium nitrite.

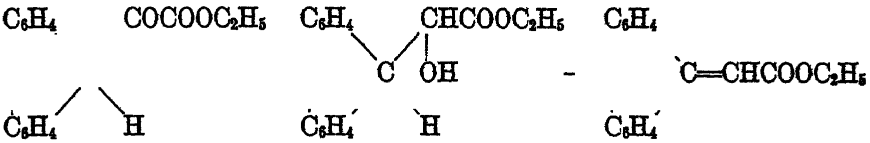


E. 9-Fluoryloxalic ester and 9-formylfluorene

In 1900 Wislicenus (337) described the condensation of ethyl oxalate with fluorene in the presence of sodium ethylate to give ethyl 9-fluoryloxalate.

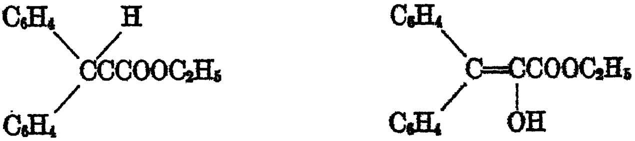


It formed intensely yellow needles. On hydrolysis it gave the acid, $(C_6H_4)_2CHCOCOOH$ (338). Reduction (283, 285, 346) with aluminum amalgam in alcoholic sodium hydroxide gave some ethyl fluorene-9-hydroxyacetate, but dehydration took place largely, giving ethyl 9-fluorylideneacetate (ethyl dibenzofulvenecarboxylate).

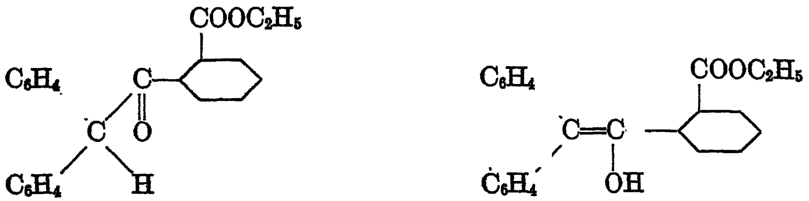


This was not unexpected, in view of Courtot's results with compounds of this same type. Reduction with zinc amalgam in dilute hydrochloric acid, however, gave an 80 per cent yield of ethyl fluorene-9-hydroxyacetate (346). Catalytic hydrogenation gave the same result (181).

Later Kuhn and Levy (181) repeated Wislicenus' condensation and were struck by the similarity of the color of ethyl 9-fluoryloxalate to that of the yellow fluorylideneacetic acid (dibenzofulvenecarboxylic acid), $(C_6H_4)_2C{=}CHCOOH$, just mentioned. Reasoning on the basis of the color relationship they were led to propose that 9-fluoryloxalic ester might have the enolic structure of α-hydroxy-β-biphenyleneacrylic ester, $(C_6H_4)_2C{=}C(OH)COOC_2H_5$. A thorough investigation supported this view, that is, that 9-fluoryloxalic ester was completely enolized in the crystalline state. The ketonic form predominated in acetic acid solution, as shown by the diminution of the yellow color and by titrations with bromine. If alkali was added to an alcoholic solution of the ester the yellow color deepened. The following tautomerism probably exists.

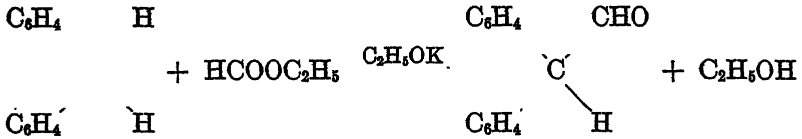


Wislicenus and Neber (341) had previously shown that a tautomerism of exactly the same type existed in the case of ethyl fluorenephthaloylate.

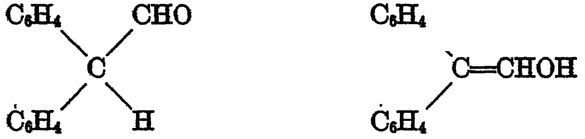


The two tautomers were capable of isolation and were interconvertible.

Wislicenus and Waldmüller (345, cf. 338) also carried out the condensation of fluorene and ethyl formate, using potassium ethylate as the



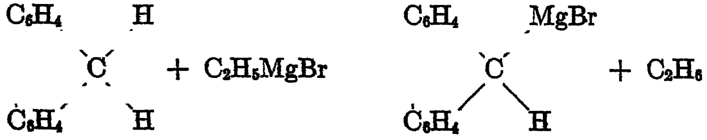
condensing agent, to give 9-formylfluorene (9-fluorylaldehyde). It formed derivatives which were characteristic of the carbonyl group (oxime, phenylhydrazone), but it also formed a derivative with phenyl isocyanate, a reagent for the hydroxyl group (342). Keto-enol tautomerism was probably present here also.



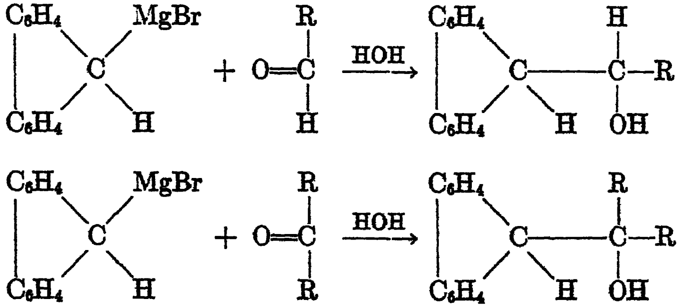
These cases of tautomerism are due to the lability of the hydrogen atom in the 9-position. We may well expect tautomerism in all compounds with a carbonyl group adjacent to the 9-carbon atom.

F. Magnesium derivatives of fluorene

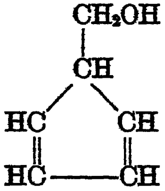
Grignard and Courtot (131) first prepared 9-fluorylmagnesium bromide by heating fluorene in toluene with ethylmagnesium bromide at 135°C.



It had all the usual properties of a Grignard reagent and reacted with aldehydes and ketones to give carbinols containing fluorene as a substituent. As previously mentioned, these carbinols are very easily dehydrated, giving derivatives of 9-methylenefluorene. For example, fluorenone reacted with the fluorylmagnesium bromide, giving an 80 per cent yield of 9-fluoryl-9-fluorenol, $(C_6H_4)_2CHC(OH)(C_6H_4)_2$, which on treating with hydrogen chloride in a boiling acetic acid solution was dehydrated to dibiphenyleneëthylene, $(C_6H_4)_2C{=}C(C_6H_4)_2$.



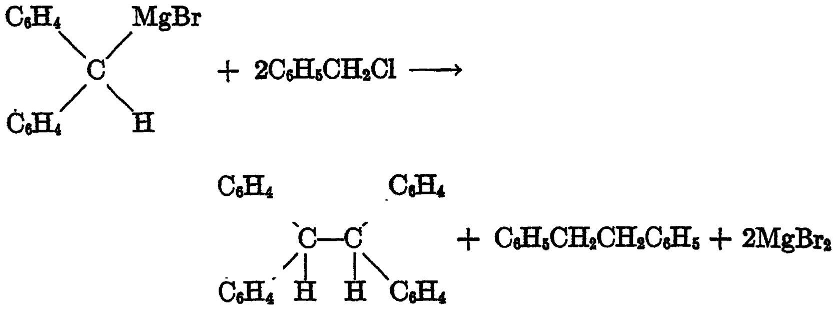
Courtot (51, 130) later extended these reactions of fluorylmagnesium bromide, using various aldehydes and ketones. He named the carbinols as derivatives of fulvanol, the alcohol of Thiele's theoretical fulvene.



Fulvanol

Thus 9-fluorylcarbinol, $(C_6H_4)_2CHCH_2OH$, was termed dibenzofulvanol. A large number of such derivatives and their dehydration products were prepared.

Quite recently Miller and Bachman (199) have studied the Grignard reagent of fluorene. They were unable to duplicate Courtot's (50) preparation of fluorylmagnesium bromide in good yields. By measuring the amount of ethane evolved the reaction was estimated to proceed to only 32 per cent of completion. When the Grignard reagent was heated with benzyl chloride the following somewhat unusual double coupling reaction occurred.

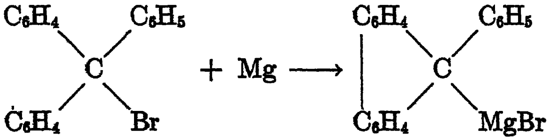


No trace of 9-benzylfluorene was found. Acetyl chloride, on the other hand, reacted normally to give 9-acetylfluorene in good yields.

Miller and Bachman's failure to obtain the Grignard reagent in good yields is not in accord with the results of Zerewitinoff (348), who treated fluorene in pyridine solution with methylmagnesium iodide at 85°C. and obtained 1.04 moles of methane. It is possible that the pyridine catalyzed the reaction. Miller and Bachman used xylene as the solvent, and Courtot used toluene.

Miller and Bachman also investigated the use of fluoryl lithium, which had been prepared earlier by Schlenk and Bergmann (257) from ethyl lithium and fluorene, and described an improved preparation (199) of this compound.[13] It reacted easily with alkyl bromides or chlorides to give 9-alkylfluorene.

The formation of the Grignard reagent of 9-bromo-9-phenylfluorene has been shown to take place in an illuminating manner (7). If 1 gram-atom of magnesium reacted with 1 mole of 9-bromo-9-phenylfluorene the Grignard reagent was formed normally.



If, however, only 0.5 gram-atom of magnesium reacted, the free radical, 9-phenylfluoryl (phenylbiphenylenemethyl), and magnesium bromide were present at the end of the reaction. On adding an additional 0.5 gram-atom of magnesium to the reaction mixture the free radical was converted to the Grignard reagent.

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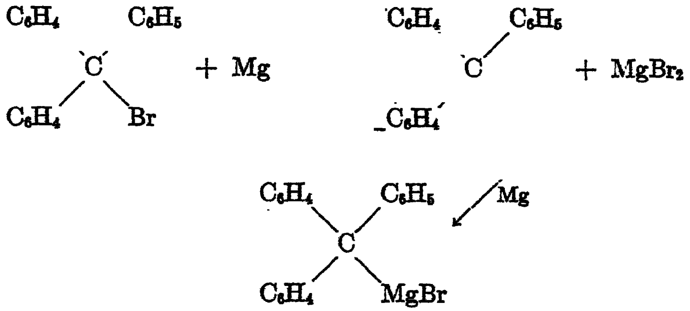
[13] Miller and Bachman regarded the lithium compound as far more useful than the Grignard reagent in this type of synthesis. It is interesting to note that they were unable to obtain sodium fluorene under usual laboratory conditions (cf. 157).

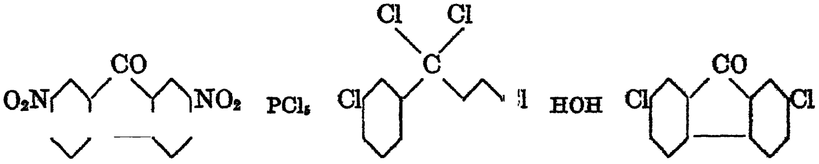


This Grignard reagent was isolated in a crystalline form and analyzed. It reacted normally with carbon dioxide and with water.

IX. NUCLEAR HALOGEN DERIVATIVES

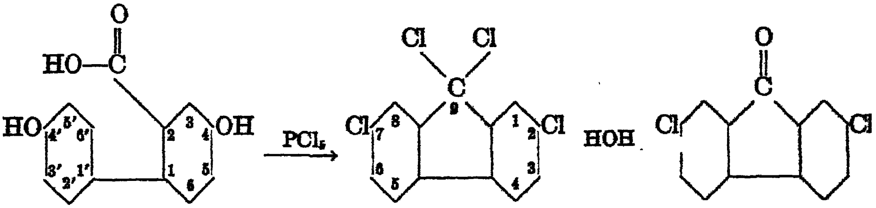
A. Chloro compounds

The first definite work on the chlorination of fluorene was done by Hodgkinson and Matthews (143). The chlorination was carried out in dry chloroform and gave a dichlorofluorene which they reported as 2,7-dichlorofluorene, m.p. 128°C. Oxidation converted it into 2,7-dichlorofluorenone, m.p. 158°C. Schmidt and Wagner (272) obtained a dichlorofluorenone by the action of phosphorus pentachloride on 2,7-dinitrofluorenone, followed by boiling the product formed with water.



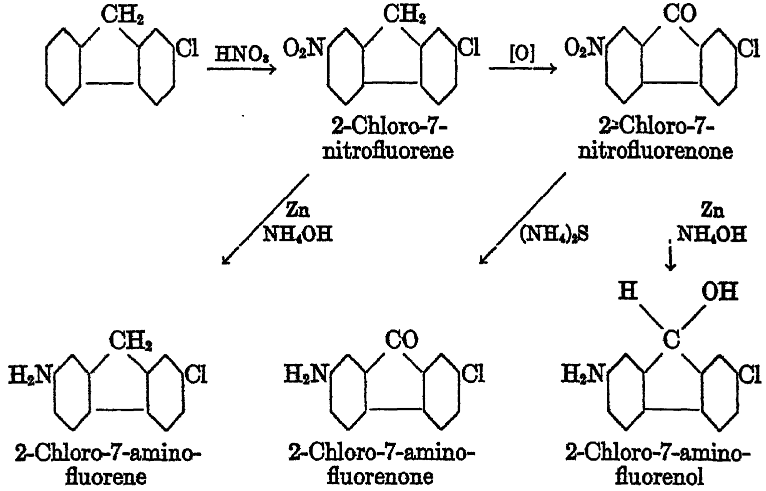
Their compound, m.p. 188°C., was interpreted as being 2,7-dichlorofluorenone. Sieglitz and Schatzkes (287, cf. 120, 32) later showed that Hodgkinson and Matthews' 2,7-dichlorofluorenone was contaminated with 2,7-dichlorofluorene.

Schmidt, Retzlaff, and Haid (267) prepared 2,7-dichlorofluorenone indirectly, thus proving that the chlorine atoms were in the 2- and the 7-positions.



4,4'-Dihydroxybiphenyl-2-carboxylic acid (55)

Courtot and Vignati (58) found that chlorination of fluorene in chloroform at 0–5°C. gave a mixture of the 2-chloro and 2,7-dichloro compounds which was very difficult to separate. Buffle (36), however, stated that 2-chlorofluorene may be obtained in a good yield by chlorinating fluorene in benzene solution at 80°C., using iodine or antimony pentachloride as a catalyst. The preparation of 2-chlorofluorene from 2-aminofluorene by the Sandmeyer reaction was reported by Courtot and Vignati and by Chanussot (40) at about the same time. Oxidation with chromic acid gave 2-chlorofluorenone. Courtot and Vignati (58) reduced the latter compound with zinc and ammonia and obtained 2-chlorofluorenol. 2,7-Dichlorofluorene behaved similarly. These authors also carried out the following reactions:



2-Chloro-7-nitrofluorene

2-Chloro-7-nitrofluorenone

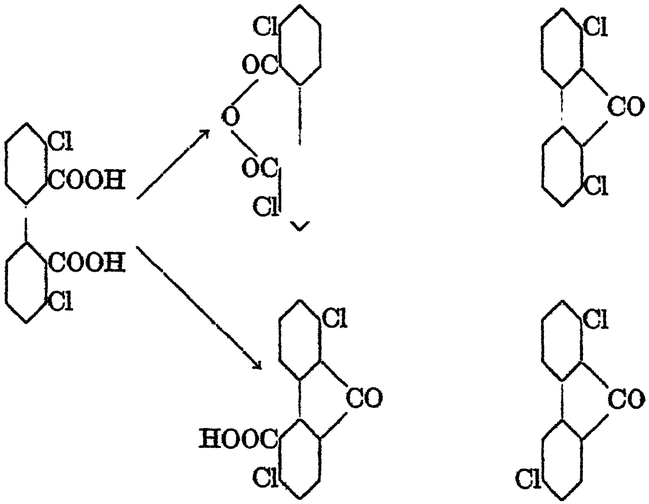
2-Chloro-7-aminofluorene

2-Chloro-7-aminofluorenone

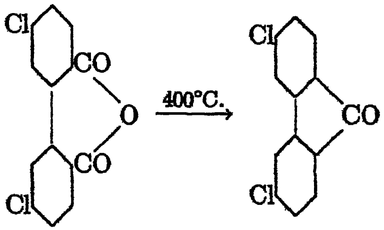
2-Chloro-7-aminofluorenol

2,7-Dichlorofluorene exhibited a greater reactivity of the methylene group than fluorene itself. Condensation with aromatic aldehydes took place with ease in the presence of a small amount of sodium ethylate (cf. page 313). Many compounds of this type have been prepared by Sieglitz and Schatzkes (287). Some of them were reduced with aluminum amalgam to the corresponding saturated compounds.

Huntress and Cliff (150) succeeded in preparing a number of dichlorofluorenones from various dichlorodiphenic acids and their anhydrides. 1,8-Dichlorofluorenone resulted in quantitative yields from the action of heat on 3,3′-dichlorodiphenic anhydride; however, when 3,3′-dichlorodiphenic acid was heated the product was 1,6-dichlorofluorenone-5-carboxylic acid, from which 1,6-dichlorofluorenone could be obtained by further heating.

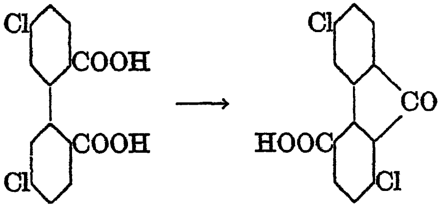


3,6-Dichlorofluorenone was obtained by the pyrolysis of 5,5′-dichlorodiphenic anhydride.

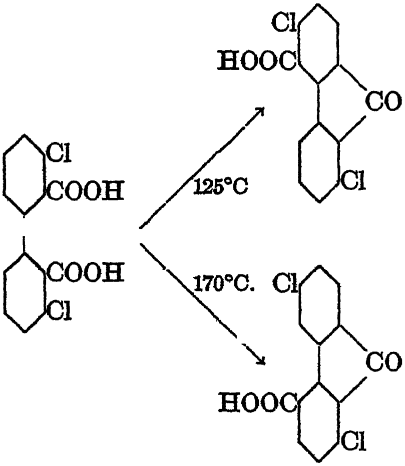


Huntress, Cliff, and Atkinson (151) extended the study of 3,3′-dichlorodiphenic acid and investigated the action of concentrated sulfuric acid upon it. At 125°C. the expected 1,6-dichlorofluorenone-5-carboxylic acid was obtained, but when the temperature was raised to 170°C. a dichlorofluorenonecarboxylic acid was obtained which was different from 1,6-dichlorofluorenone-5-carboxylic acid. In other words, "two isomeric monobasic acids are prepared at different temperatures by the same procedure from the same starting material, when the conventional theory will account for only one." They termed the isomer formed at 170°C. "Acid X." The most curious fact of all is that both isomers had exactly the same melting point (242.5°C.), but the melting point of a mixture of equal parts was approximately 200°C. and their acid chlorides melted at different temperatures. Two other interesting facts were noted. On redissolving 1,6-dichlorofluorenone-5-carboxylic acid in sulfuric acid and heating at 170°C., "Acid X" was formed in a 67 per cent yield. The carboxyl group of "Acid X" was removed and the product was found to be 1,6-dichlorofluorenone, showing "that during the isomerization to 'Acid X' both the fluorenone nucleus and the relative position of the two halogen atoms in it are preserved."

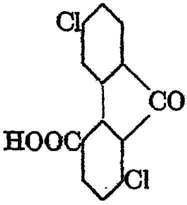
Three years later Huntress and Atkinson (148) were able to establish the constitution of "Acid X" as that of 1,6-dichlorofluorenone-4-carboxylic acid. The acid proved to be identical with the compound obtained by the action of concentrated sulfuric acid on 5,5'-dichlorodiphenic acid. The reaction giving the isomeric acid was thus shown to involve the migration of the halogens. This emphasizes the danger in the use of high temperatures in the synthesis of fluorenones.

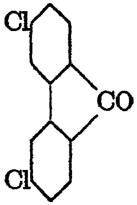


"Acid X"

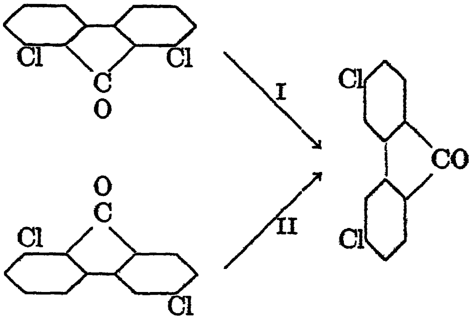


On attempting to decarboxylate 1,6-dichlorofluorenone-4-carboxylic acid by heating in sulfuric acid it was noted that 3,6-dichlorofluorenone was formed.





Further experiments showed that both 1,8-dichlorofluorenone and 1,6-dichlorofluorenone rearranged to 3,6-dichlorofluorenone on heating in sulfuric acid at 185–200°C.



These rearrangements are unusual, for in rearrangement II the one chlorine atom migrated to a position meta to its original position, and in rearrangement I both chlorine atoms did so. Rearrangements involving meta transpositions are rare, and it seems curious that Huntress and Atkinson did not point this out. It is also noteworthy that the position taken is para to the carbonyl group and meta to the phenyl.

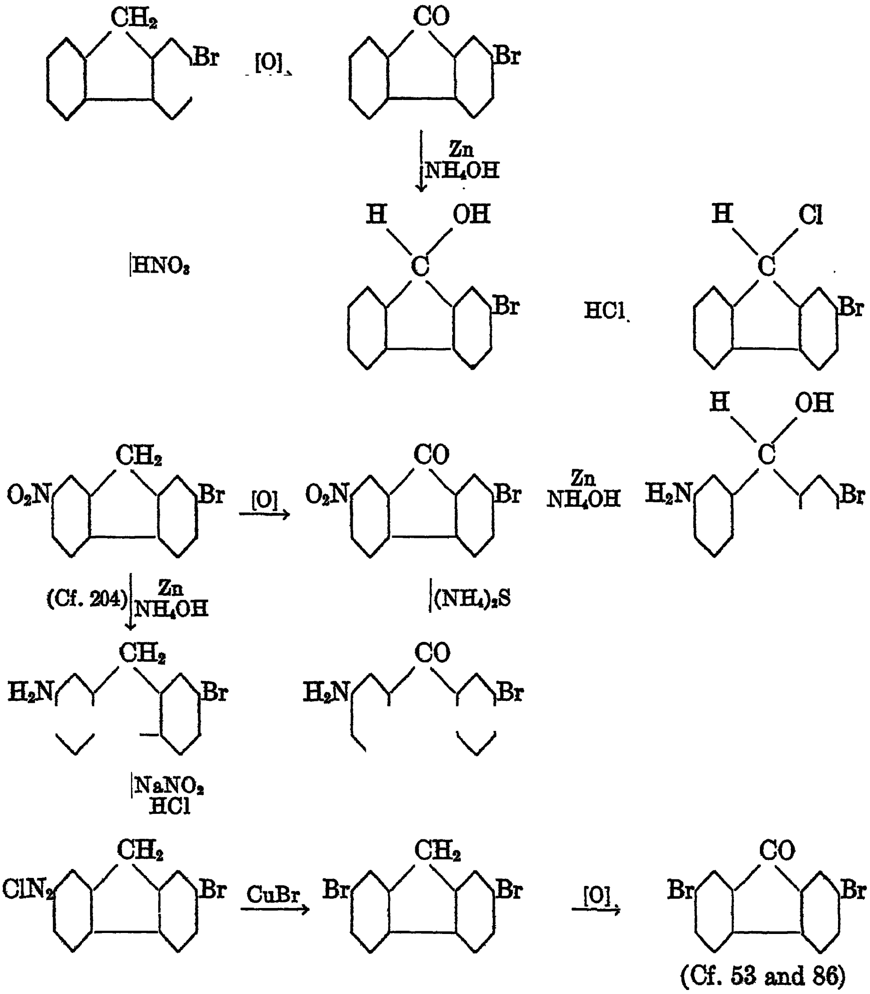
More highly chlorinated compounds, whose orientation is unknown, have been recorded. Holm (145) prepared a trichlorofluorene, m.p. 147°C., by chlorinating fluorene in carbon disulfide. Hodgkinson and Matthews (143) described a "pentachlorofluorenedichloride," $C_{13}H_5Cl_7$, which they obtained in an impure state by chlorinating fluorene in carbon tetrachloride in the presence of iodine. On attempting to carry out an alkali fusion of this compound they encountered serious explosions. Alcoholic potash reacted to give a compound containing fewer chlorine atoms.

B. Bromo compounds

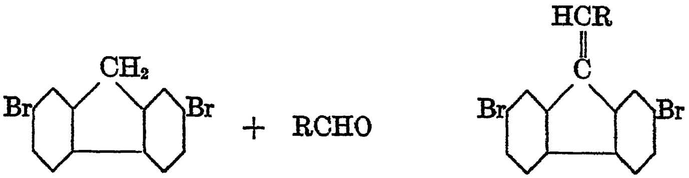
The bromination of fluorene results in the formation of 2-bromofluorene and 2,7-dibromofluorene (12, 15, 46, 143, 145, 282, 313). A synthetic proof of the position of the bromine atom was embodied in the preparation of the corresponding bromofluorenones from the proper phenanthraquinone derivatives (261). Courtot and Vignati (59) prepared 2-bromofluorene from 2-aminofluorene by the Sandmeyer reaction. These authors showed also that bromine entered the same positions when fluorenone is brominated, and also that the bromine atom in 2-bromofluorene may be replaced by an amino group by reaction with ammonia in the presence of copper salts.

The mixture of 2-bromofluorene and 2,7-dibromofluorene obtained in the bromination proved very difficult to separate (175). Courtot obtained a good separation only after ten recrystallizations from 90 per cent alcohol. Clarkson and Gomberg (46) and Miller and Bachman (199), however, obtained a very good separation by distillation *in vacuo*.

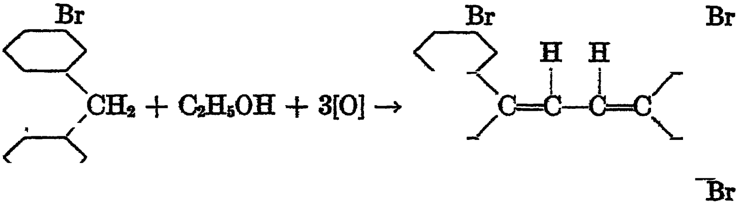
Courtot and Vignati (59) have carried out numerous reactions with 2-bromofluorene, as shown by the following equations:



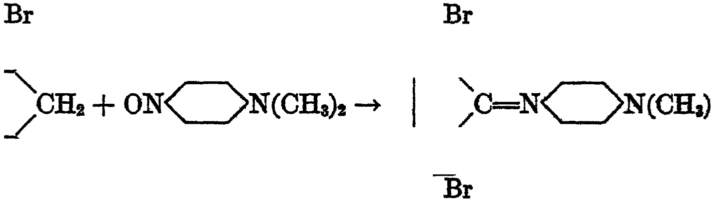
The introduction of the two bromine atoms into the nucleus also enhanced the reactivity of the methylene group. Sieglitz (282b, cf. 182) prepared an impressive list of derivatives by condensing aromatic aldehydes with 2,7-dibromofluorene in alcoholic solution in the presence of sodium ethylate.



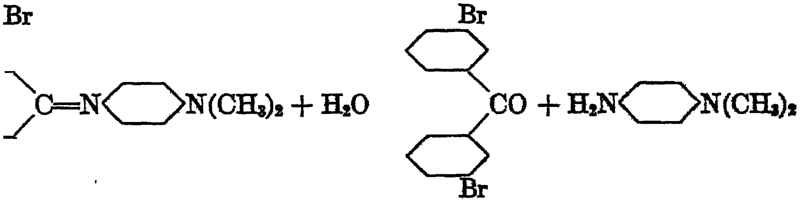
As a by-product of each preparation Sieglitz obtained a small amount of *sym*-tetrabromobiphenylenebutadiene. Stahrfoss (291) showed that it was formed according to the following equation:



Novelli (219) prepared several azomethines by condensing nitroso compounds with 2,7-dibromofluorene, for example, by condensing *p*-nitrosodimethylaniline with 2,7-dibromofluorene in the presence of sodium ethylate.

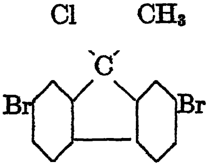


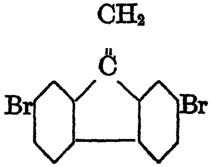
The various azomethines were highly colored and were very sensitive to acids, hydrolysis taking place readily. The yield of 2,7-dibromofluorenone was nearly quantitative, and Novelli recommended this procedure as being more satisfactory than the usual dichromate oxidation.



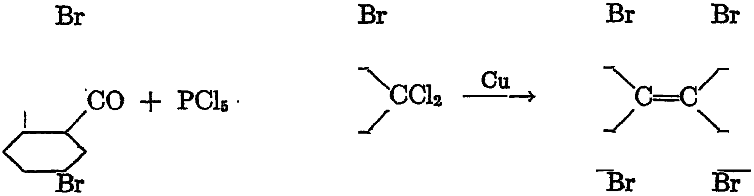
Sieglitz (283) found that 2,7-dibromofluorene, like fluorene, condensed with ethyl oxalate but with more ease, to give ethyl 2,7-dibromo-9-fluoryloxalate. He then carried out some syntheses with this compound analogous to those previously described.

The enhanced reactivity of groups in the 9-position of 2,7-dibromofluorene is apparent in that 9-methyl-9-chloro-2,7-dibromofluorene may lose hydrogen chloride to give 9-methylene-2,7-dibromofluorene (286).





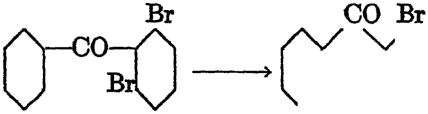
Schmidt and Wagner (272) synthesized various dimeric compounds from 2,7-dibromofluorenone and 2-bromofluorenone in the following manner:



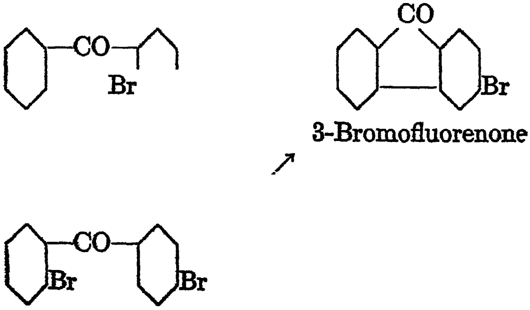
2,7-Dibromofluorenone
2,7-Dibromo-9,9-dichlorofluorene
2,2′,7,7′-Tetrabromodibiphenyleneëthylene

The dibiphenyleneëthylene derivative could be reduced catalytically to the corresponding ethane. Chlorine and bromine also added readily to the double bond.

Other bromo compounds in addition to the 2- and the 2,7-derivatives have been prepared. Montagne and Charante (203, 204) synthesized bromofluorenones from bromobenzophenones by boiling them in alcohol for several days.

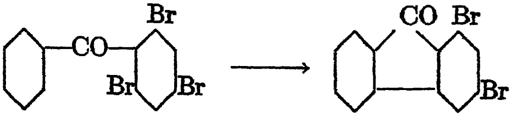


1-Bromofluorenone



3-Bromofluorenone

These reactions are impracticable as methods of preparation, as the yields are very small. Montagne (203) prepared 1,3-dibromofluorenone in a similar way from 2,4,6-tribromobenzophenone. Heating at a temperature of 400°C. for several days was necessary.



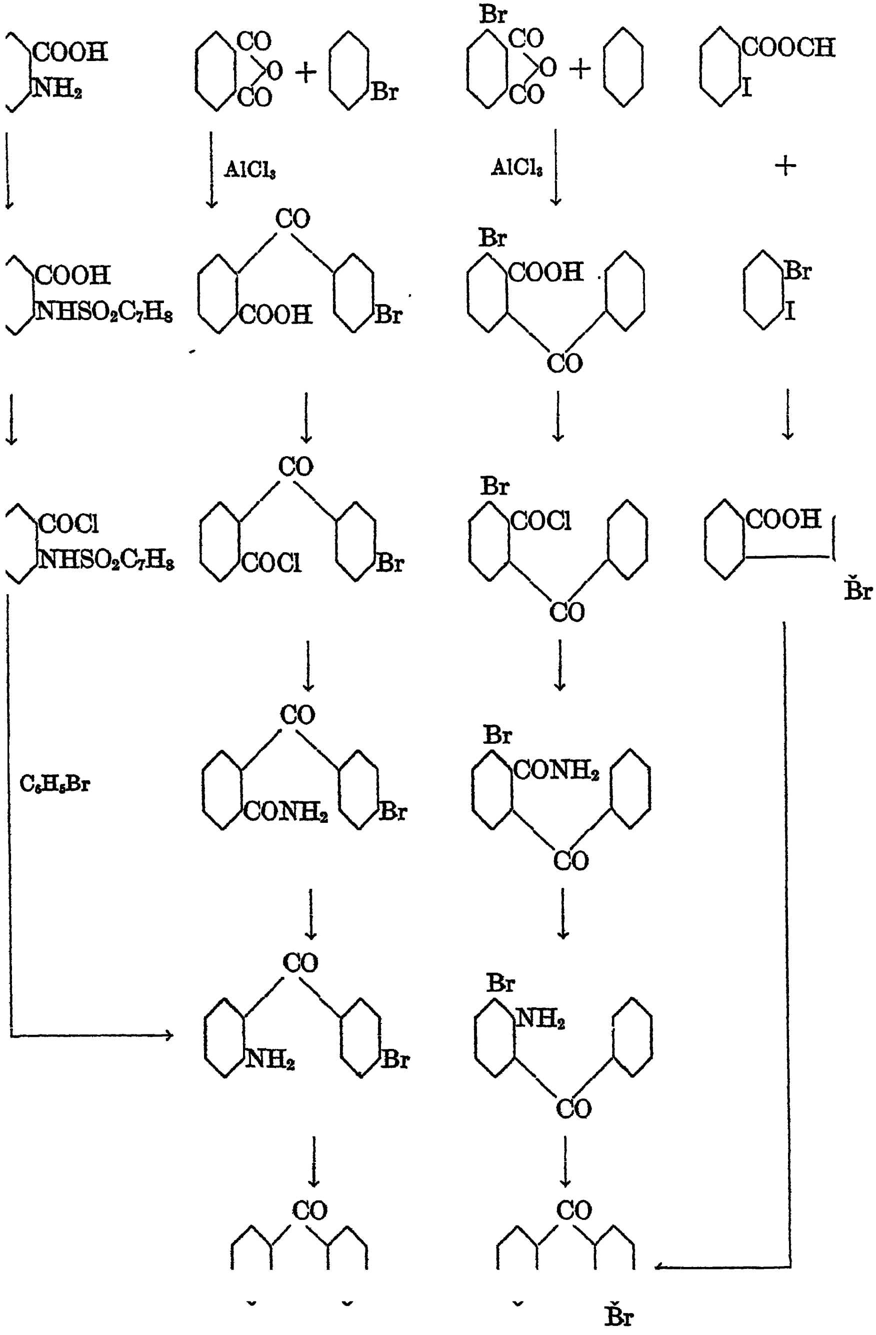
1,3-Dibromofluorenone

The bromine atoms in 1,3-dibromofluorenone are very labile, for on reduction with sodium amalgam only fluorenol is obtained.

Miller and Bachman (200) recently described nuclear syntheses for 3- and 4-bromofluorenones which were suitable for preparative purposes, since they did not require such difficultly obtainable intermediates as was the case with Montagne's method; moreover, the yields were reported to be fairly good despite the number of steps involved. (See formulae on page 344.) Miller and Bachman pointed out that by the application of these methods dibromofluorenones which are yet unknown can be synthesized. The yield of 3-bromofluorenone from phthalic anhydride was 55 per cent and from anthranilic acid 21 per cent. 4-Bromofluorenone was obtained in a 14 per cent yield from methyl-*o*-iodobenzoate and in a 25 per cent yield from bromophthalic anhydride. The last two intermediates were rather difficult to obtain and the syntheses are not so generally applicable. Miller and Bachman found, however, that 4-bromofluorene, which yielded the fluorenone on oxidation, could be obtained in good yields by another method which will be discussed later.

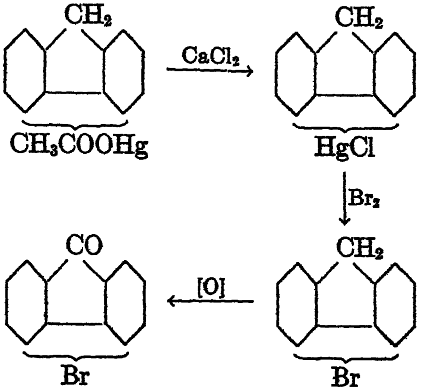
Reduction of the two bromofluorenones (3- and 4-) with zinc dust gave the corresponding fluorenols in excellent yields. The fluorenols could then be reduced to the fluorenes with amalgamated zinc and hydrochloric acid. The lability of the bromine atom in the 3-position noticed by Montagne was also found by Miller and Bachman, for 3-bromofluorenol on reduction with hydriodic acid and phosphorus gave only fluorene. These authors stated that this lability was remarkable "in view of the equally great stability of the bromine atom in the 2-position." Experiments showed that 2-bromofluorene did not yield a Grignard reagent (199) and also that it was only about 50 to 75 per cent as reactive as bromobenzene, as shown by its behavior with potassium phenolate and sodium acetate (186). Miller and Bachman stated that the contrast between the 2-bromo- and the 3-bromo-fluorenes is reminiscent of the somewhat similar contrast in stability offered by the 1-bromo- and the 2-bromo-naphthalenes.

Miller and Bachman also determined the positions in which fluorene mercurates (201). Knowing the properties of all the four possible mono-



3-Bromofluorenone 4-Bromofluorenone

bromofluorenones they could easily determine the position in which mercuration took place by the following scheme:



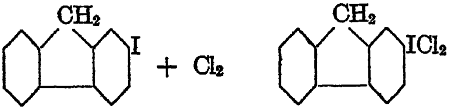
Applying this method they found that fluorene in the presence of acetic acid mercurated in the 4-position, but in the absence of solvents some of the 3-isomer was formed. Fluorene-4-mercuric acetate, when treated with alcoholic calcium chloride, gave fluorene-4-mercurichloride which on subsequent bromination yielded 4-bromofluorene, thus providing a simple synthesis for this isomer. 3-Bromofluorene was obtained in a similar manner from fluorene-3-mercuriacetate. Neither of the two mercury compounds prepared by Miller and Bachman corresponded to the mercury compound reported by Goswami and Das Gupta (123), who used the same method of mercuration.

More highly brominated fluorene compounds have been reported, but their constitution is unknown. A tribromofluorene and a tetrabromofluorene have been described by Barbier (15). Schmidt and Bauer (261) obtained a tribromofluorene which on oxidation yielded a tribromofluorenone identical with the compound prepared by brominating 2,7-dibromofluorenone. The position of the third bromine atom is doubtful. Eckert and Langecker (87) brominated 2-aminofluorene and obtained tribromo-2-aminofluorene. On oxidation and removal of the amino group a tribromofluorenone was obtained. They also brominated some 2-methoxy compounds.

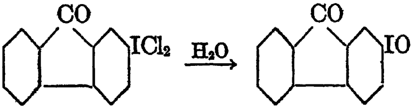
C. Iodo and fluoro compounds

Work upon iodine-substituted compounds is still in the preliminary stages, as only the 2-iodofluorene is known. Chanussot (39) and Courtot (53) have prepared 2-iodofluorene from the diazo compound. Oxidation with dichromate and acetic acid gave 2-iodofluorenone.

Chanussot (41) carried out reactions with 2-iodofluorene and 2-iodofluorenone analogous to those undergone by iodobenzene. Fluorene-2-iodo dichloride was prepared in quantitative yields by passing chlorine into a chloroform solution of 2-iodofluorene.



The dichloride decomposed at 70–75°C. to a white substance which was probably 2-iodo-7-chlorofluorene. 2-Iodofluorenone formed a similar dichloride. On shaking fluorenone-2-iodo dichloride with pyridine and water good yields of 2-iodosofluorenone were obtained.



Fluorene-2-iodo dichloride reacted similarly, giving 2-iodosofluorene. Both 2-iodofluorene and 2-iodofluorenone were oxidized by hypochlorous acid to the corresponding iodoxycompounds which exploded violently on heating.

Bergmann, Hoffman, and Winter (27) prepared 2-fluorofluorene and 2-fluorofluorenone from the amines by the diazo reaction, using fluoroboric acid. 2-Fluorofluorenone reacted with phosphorus pentachloride to give 9,9-dichloro-2-fluorofluorene, which could be used to synthesize the usual dimeric compounds.

The only other known fluoro compound was prepared by Stoughton and Adams (303) from 2-nitro-6-carboxy-2′-fluoro-5′-methylbiphenyl (see page 300).

As can be seen, much remains to be done on the iodine and fluorine derivatives.

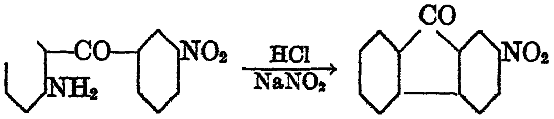
X. NITRO AND AMINO COMPOUNDS

A. Mononitro and monoamino compounds

The nitration of fluorene has received considerable attention from a number of investigators. During the course of their researches many conflicting statements have been made. At the present time, however, the structures of the majority of the compounds are known with reasonable certainty.

The first product formed on the nitration of fluorene or fluorenone proved to be the 2-nitro compound (15, 27, 71, 111, 205, 209, 261, 280, 304).

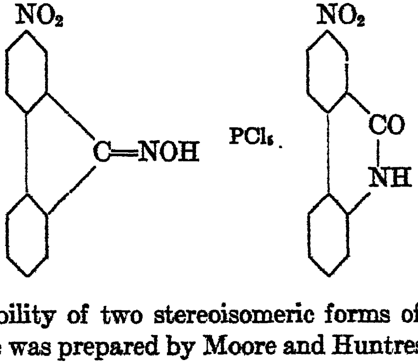
A convenient preparation of 2-nitrofluorene has been described by Kuhn (221) and is based on the procedure of Diels (71). 2-Nitrofluorene crystallized from hot glacial acetic acid in light yellow prisms, m.p. 157°C. Oxidation with chromic acid or permanganate gave 2-nitrofluorenone, m.p. 217–218°C. Ullmann and Mallett (316) prepared it indirectly by diazotizing 2-amino-3-nitrobenzophenone.



Gerhardt (111) prepared the hydrazone, which on long boiling in alcohol gave 2-nitrofluorenone ketazine.

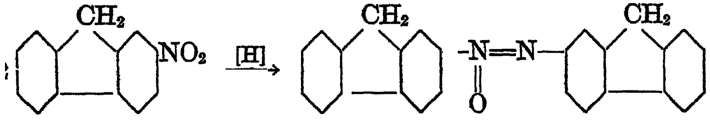
2-Nitrofluorene, like fluorene, will condense with aromatic aldehydes. Loëvenich and Loeser (187) carried out a long series of these condensations, using sodium ethylate as the condensing agent. Candea and Macovski (37) extended this work, using piperidine as the condensing agent.

Moore and Huntress (206) prepared 2-nitrofluorenone-5-carboxylic acid by the action of concentrated sulfuric acid on 4-nitrodiphenic acid. It was a pure yellow substance. By means of the Hofmann reaction 5-amino-2-nitrofluorenone, deep scarlet in color, was prepared. The same authors showed that the oxime of 2-nitrofluorenone underwent a normal Beckmann rearrangement and gave a 90 per cent yield of 7-nitrophenanthridone (206). This was, therefore, the *syn*-form.



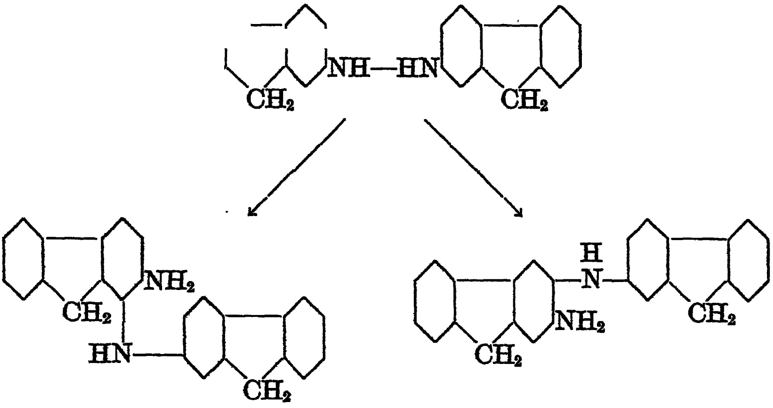
There is a possibility of two stereoisomeric forms of 2-nitrofluorenone oxime. The oxime was prepared by Moore and Huntress from fluorenone, hydroxylamine hydrochloride, and alcohol (representing an acid solution) and had a melting point of 262.5–263°C. Langecker (183, cf. 149) prepared the oxime in the same way, but used in addition barium carbonate (i.e., a neutral solution), and found the melting point to be 249°C. This may well be the *anti*-form.

Cislak, Eastman, and Senior (44) investigated the reduction of 2-nitrofluorene using Diels' method (zinc, dilute alcohol, and calcium chloride), but employed only one-tenth the usual amount of zinc. The product of



this reaction was reported to be 2,2′-azoxybisfluorene, m.p. 279°C. This compound was characterized by its almost complete insolubility in ordinary organic solvents; by virtue of this insolubility it escaped further reduction, as shown by attempts to reduce a suspension of it in alcohol with zinc and acetic acid. An attempt was made to oxidize it to the corresponding fluorenone, using dichromate and acetic acid, but even prolonged boiling caused no oxidation. This is very unusual in view of the fact that all other fluorene compounds are oxidized to the corresponding fluorenones under these conditions.

The compound was found, however, to be soluble in phenol, in which it was reduced with zinc and hydrochloric acid. The main product was 2-aminofluorene, but in addition a small amount of another substance was formed. It was proved that the substance was not 2,2′-hydrazobisfluorene or 2,2′-azobisfluorene. They concluded that the hydrazo compound was formed during reduction and then had undergone a rearrangement of the *o*-semidine type. The following two compounds were then possible.



2–Amino–1,2′–difluorylamine   2′–Amino–2,3′–difluorylamine

There is no evidence as to which was the correct formula, but an investigation of the compounds formed on acetylation showed that it was either one or the other. Cislak, Eastman, and Senior made the statement that

2-nitrofluorene when boiled with ammonium sulfide was not reduced to the amino compound, while 2-nitrofluorenone under the same conditions was easily reduced to 2-aminofluorenone. Courtot and Vignati reported the reduction of 2-chloro-7-nitrofluorene to the corresponding amine by ammonium sulfide as previously stated.

The complete reduction of 2-nitrofluorene gave 2-aminofluorene, which crystallized in straw-colored needles melting at 127°C. It was first prepared by Strasburger (304) from 4-aminodiphenic acid. Diels (71) used zinc dust and calcium chloride with dilute alcohol to reduce 2-nitrofluorene, while Austin (6) employed stannous chloride in acid solution. Bennett and Noyes (22) have reported excellent yields of 2-aminofluorene, using catalytic reduction with hydrogen and platinum oxide. Diels (71) prepared a number of derivatives (cf. 21) of 2-aminofluorene, such as 2-fluorenediazonium chloride, which crystallized out as small yellow crystals and was stable in warm water, but on boiling decomposed to 2-hydroxyfluorene. The hydrazine was prepared from the diazo compound by reduction with sodium bisulfite.

A quinoline derivative was prepared by Diels and Staehlin (73) from 2-aminofluorene. Later Loevenich and Loeser (188) and I. Kh. Fel'dman (93) extended this work.

Ray and Rieveschl have prepared 2-isocyanofluorene from 2-aminofluorene and phosgene; it reacted instantly with amines and alcohols to give ureas and urethans of fluorene (241).

The reduction of 2-nitrofluorenone to 2-aminofluorenone has usually been accomplished with ammonium sulfide (21, 22, 71, 111); other reducing agents also reduce the carbonyl group in the 9-position. 2-Aminofluorenone is a deep red compound melting at 163°C. The diazo compound is unusually stable and may be crystallized from warm water. It decomposes, when dry, at 128°C. Diazo compounds of both 2-fluorene and 2-fluorenone react normally in the Sandmeyer reaction (53).

Several other mononitro derivatives involving other than the 2-position are known. 1-Nitrofluorenone is at present unknown; however, 1-aminofluorenone was prepared by Goldschmiedt (117) from fluorenone-1-carbonamide by the Hofmann reaction. It is interesting to note that only a very few 1-substituted fluorenones or fluorenes have been prepared, despite the fact that as early as 1902 Goldschmiedt provided the basis for the synthesis of a great number of such derivatives.

Eckert and Langecker (87) prepared 3-nitrofluorenone by the deamination of 2-amino-3-nitrofluorenone (the preparation of which will be discussed later). They converted their supposed 3-nitrofluorenone to the amine and thence to the known 3-hydroxyfluorene, thus proving its structure. They gave the melting point of 3-nitrofluorenone as 210°C. This agrees with the value reported by Schmidt and Soll (269), who obtained it from 3-nitrophenanthraquinone by the benzilic acid rearrangement followed by oxidation. The latter authors prepared the oxime by heating the ketone and hydroxylamine hydrochloride together in alcoholic solution. They obtained a compound, melting at 240°C., which analyzed correctly for nitrogen.

Bardout (16) prepared 3-nitrofluorenone, both by Eckert and Langecker's method and by a modified method, and reported it as melting at 232°C. (239°C., corr.). He converted it to the known 3-hydroxyfluorenone (90) and to the methoxyfluorenone (314). The bromo derivative was reported as melting at 165.5°C. (corr.). Miller and Bachman (200) gave a melting point of 162°C., apparently uncorrected. Bardout's oxime melted at 217°C. (221°C., corr.). Bardout failed to find any trace of a possible isomer.

Two Japanese investigators, Hayashi and Nakayama (138), have confirmed Bardout's preparation of 3-nitrofluorene, but did not oxidize it to the fluorenone. They reduced it to 3-aminofluorene, m.p. 151.5–152°C., by means of stannous chloride.

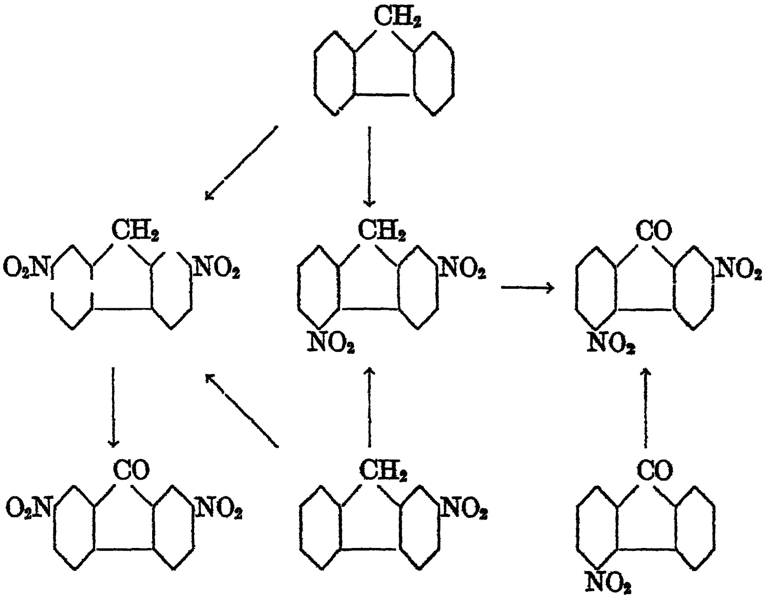
No decision can be made between the two conflicting values, but it is unusual for an oxime to melt lower than the ketone.

Schmidt and Bauer (261a) obtained 4-nitrofluorenone from 4-nitrophenanthraquinone in the usual manner. Courtot (53, cf. 209) later improved the preparation of 4-nitrophenanthraquinone. He gave the melting point of 4-nitrofluorenone as 135°C. Reduction with ammonium sulfide yielded 4-aminofluorenone, and with zinc and acid, 4-aminofluorenol.

2-Bromo-9-nitrofluorene was used by Thurston and Shriner (313) in an attempt to establish the asymmetry of the *aci*-nitro link. A small but definite rotation was reported for the unpurified potassium salt. 2-Bromofluorene reacted with *d*-2-octyl nitrate in the presence of potassium ethylate (cf. page 309) to give the salt of 2-bromo-9-*aci*-nitrofluorene.

B. Dinitro and diamino compounds

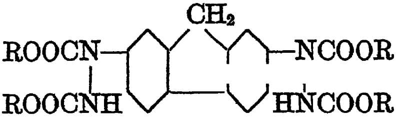
This phase of the chemistry of fluorene has been investigated with some thoroughness, affording varied results. It has been generally agreed that mononitration of fluorene gives 2-nitrofluorene in good yields. When nitration was carried beyond the mononitro stage, 2,5-dinitrofluorene (209), melting at 207°C., and 2,7-dinitrofluorene, which decomposes at 295–300°C., were obtained. The latter isomer was formed in a 66 per cent yield (3) and the former in a 22 per cent yield (45, 53). A similar result was obtained when 2-nitrofluorene was nitrated, 2,5- and 2,7-dinitrofluorenes being the products. Anantakrishnan and Hughes carefully checked these results. Oxidation of the two isomers yielded 2,5-dinitrofluorenone, m.p. 241°C., and 2,7-dinitrofluorenone, m.p. 292°C. Gallas (110) condensed 2,7-dinitrofluorenone and 2,7-dinitrofluorene in the presence of zinc chloride to obtain 2,7,2′,7′-tetranitrodibiphenylene-ethylene, which could be reduced to the corresponding tetraamino compound. Morgan and Thomason (209) established the constitution of 2,5-dinitrofluorenone by nitrating 4-nitrofluorenone (positions 4 and 5 are identical in monosubstituted compounds). The following equations represent these reactions:



Morgan and Thomason made the statement that the second nitro group is directed by the phenylene radical, thus entering the second ring in the ortho and para positions (positions 5 and 7).

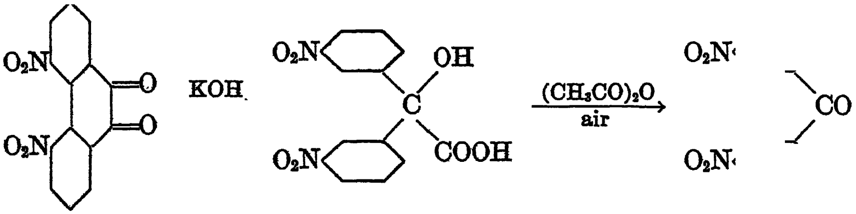
The dinitro compounds just described may be reduced to the corresponding diamino compounds. 2,7-Diaminofluorene is the best known diamine. Schultz (279) had established its structure by showing that it was formed in the distillation of 4,4′-diaminodiphenic acid with lime (72). It crystallized in needles, m.p. 165°C., which were nearly colorless, but darkened on standing a short time. Its use in analytical chemistry will be discussed later. 2,5-Diaminofluorene is a pinkish white substance melting at 175°C. (209). Solutions of it give an olive-green color with ferric chloride.

Stollé and Adam (300) reported a unique method for the preparation of 2,7-diaminofluorene. They added azodicarboxylic esters to fluorene. On reduction with hydriodic acid these gave 2,7-diaminofluorene.

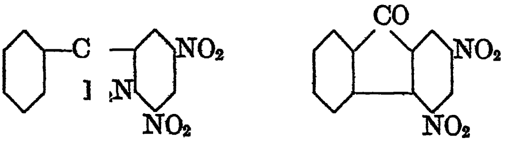


Courtot (53, cf. 267, 280) studied the reduction of 2,5- and 2,7-dinitrofluorenones. Reduction with zinc and ammonium hydroxide gave the diaminofluorenols, while ammonium sulfide affected only the nitro groups, giving the diaminofluorenones. Courtot remarked that the colored derivatives of aminofluorenols were more intensely colored than the corresponding derivatives of aminofluorenones; for example, 2,5-diaminofluorenone was brownish red, while 2,5-diaminofluorenol was deep red.

4,5-Dinitrofluorenone has been prepared by Schmidt and Bauer (261a) from 4,5-dinitrophenanthraquinone. It crystallized in yellow needles which did not melt at 350°C. No study of the reduction of this compound has been reported.



Ullmann and Broido (315) prepared 2,4-dinitrofluorenone indirectly by diazotizing 2-amino-3,5-dinitrobenzophenone with sodium nitrite in concentrated sulfuric acid. It formed yellow needles which melted at 197°C.



Wislicenus and Weitemeyer (346b) showed that nitration of ethyl fluorene-9-glyoxalate in acetic acid gave a 90 per cent yield of 2,9-dinitrofluorene. Heating this compound above its melting point resulted in the formation of 2-nitrofluorenone. The same dinitro compound was obtained by the action of nitric acid on 9-nitrofluorene or ethyl 2-nitrofluorene-9-glyoxalate. Bennett and Noyes (22) obtained the corresponding diamine

(2,9-diaminofluorene) by reducing 2-aminofluorenone hydrazone with zinc and acid. All attempts to condense 2-nitrofluorene with ethyl nitrate to give 2-nitro-9-*aci*-nitrofluorene failed (346b). It also refused to condense with esters of formic acid.

Rose (247) has carried out nitration experiments with fluorene-9-carboxylic acid. He obtained 2-nitrofluorene-9-carboxylic acid, 2,7-dinitrofluorene-9-carboxylic acid, and 2-nitro-7-sulfofluorene-9-carboxylic acid.

Schmidt and Stützel (270b), and later Kuhn and Jacob (179), investigated the nitration of 9-acetylaminofluorene. The first group of investigators characterized the dinitrofluorenone which they obtained as 1,8-dinitrofluorenone, on the basis of the products of oxidation. Kuhn and Jacob apparently confirmed these results.

Langecker (183) in 1931, seeking to prepare 1- or 1,8-substituted products of fluorenone, reinvestigated the nitration of 9-acetylaminofluorene. He found the main product of the nitration to be 2-nitrofluorenone. Huntress and Cliff (149) then undertook a critical examination of the work of Schmidt and Stützel. A recalculation of the analytical data given by Schmidt and Stützel for 1,8-dinitrofluorenone showed that the nitrogen content of the compound was not 10.40 per cent, but really only 8.08 per cent. The value is 6.22 per cent for a mononitrofluorenone and 10.36 per cent for a dinitrofluorenone. Schmidt and Stützel reported that on oxidation *o*-nitrobenzoic acid was obtained. Huntress and Cliff pointed out the proximity of the melting points of *o*- and *m*-nitrobenzoic acids. Even though *o*-nitrobenzoic acid were obtained, it would only account for the position of one of the nitro groups. Using the exact conditions of Schmidt and Stützel in four separate experiments, these authors obtained 70 per cent yields of 2-nitrofluorenone. Carrying the nitration further they obtained 2,7-dinitrofluorenone and a new dinitrofluorenone, m.p. 213–214°C., which was neither 2,4- nor 2,5-dinitrofluorenone. It is thus seen that the question is still unsettled.

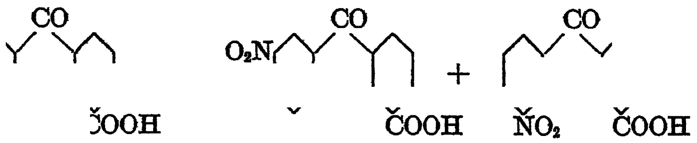
Anantakrishnan and Hughes (3) recently studied the nitration of 9-bromofluorene. Mild treatment with nitric acid in acetic anhydride resulted in the formation of 9-bromo-2-nitrofluorene, m.p. 145°C. This compound was identical with the compound formed by the bromination of 2-nitrofluorene (175). Two products were obtained by using a stronger nitrating mixture; they were separable by fractional crystallization from acetone. These two compounds were identified as 9-bromo-2,7-dinitrofluorene, m.p. 255°C., and 9-bromo-2,5-dinitrofluorene, m.p. 199°C., by oxidation to the corresponding dinitrofluorenones, the bromine atom being removed during the oxidation. A similar result was obtained by nitrating 9-bromo-2-nitrofluorene. From the several cases just described it seems that substituents in the 9-position have no effect upon the position taken by the entering nitro group; in other words, the same positions are involved whether fluorene itself or a 9-substituted derivative is nitrated.

Diels, Schill, and Tolson (72), continuing their work on the nitration of fluorene, investigated the action of nitric acid on 2-acetylaminofluorene. A mixture of two mononitro compounds was obtained. Saponification yielded two aminonitrofluorenes which were widely different in basicity. The more basic one was found to be 2-amino-7-nitrofluorene, as shown by reduction to the known 2,7-diaminofluorene. The less basic compound was reported as 2-amino-1-nitrofluorene. Twenty-six years later Eckert and Langecker (87) showed that this compound was really 2-amino-3-nitrofluorene. The position of the nitro group was determined by first oxidizing the nitration products to the corresponding nitroacetylaminofluorenones and then hydrolyzing. 2-Amino-7-nitrofluorenone (45, 138) was removed by extraction with hydrochloric acid. The residue, 2-amino-3-nitrofluorenone, on deamination yielded the known 3-nitrofluorenone, which was in turn reduced to the known 3-aminofluorenone and then through the diazo compound to 3-hydroxyfluorenone. (See page 355.) 2-Amino-3-nitrofluorenone on reduction with sodium sulfide gave 2,3-diaminofluorenone, which showed characteristic reactions of an orthodiamine.

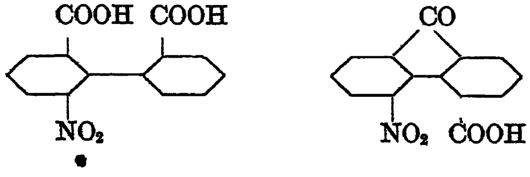
Eckert and Langecker (87) also investigated the nitration of other derivatives of fluorene involving the 2-position. 2-Acetylaminofluorenone gave results analogous to 2-acetylaminofluorene. 2-Aminofluorenone, however, gave only 2-amino-7-nitrofluorenone.

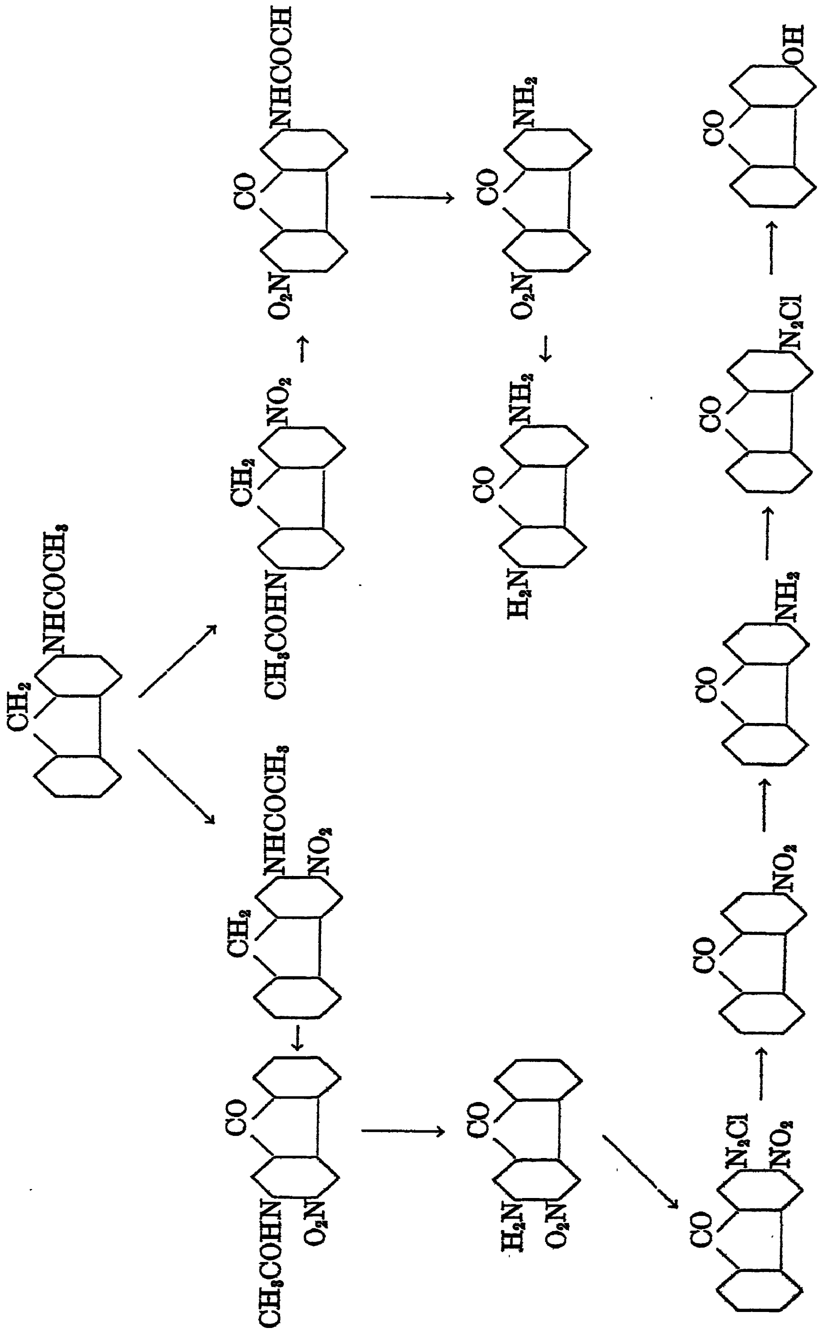
Ruiz (249) nitrated 2-methoxyfluorene, using Eckert and Langecker's method, to 2-methoxy-3-nitrofluorene. His experiments on the nitration of 2-hydroxyfluorene gave uncertain results; the nitro group, however, was shown to be in the same ring as the hydroxyl group.

The nitration of fluorenone-4-carboxylic acid resulted in approximately equal amounts of 7-nitrofluorenone-4-carboxylic acid (2-nitrofluorenone-5-carboxylic acid) and 5-nitrofluorenone-4-carboxylic acid (206).

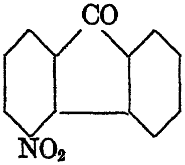


The latter compound may be prepared by heating 6-nitrodiphenic acid with concentrated sulfuric acid (19, 206).

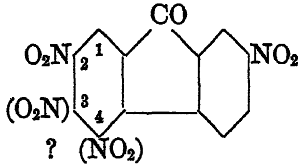


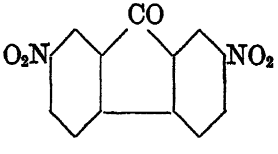

CH₂
NHCOCH₃
CH₂
CH₃COHN
NO₂
CO
O₂N
NHCOCH
CO
O₂N
NH₂
CO
H₂N
NH₂
CO
OH
CO
N₂Cl
CO
NH₂
CO
NO₂
CH₂
NHCOCH₃
NO₂
CO
CH₃COHN
O₂N
CO
H₂N
O₂N
CO
N₂Cl
NO₂

The question of the orientation of any trinitro compounds is still unsettled. Schmidt (261b, 267) and his coworkers reported the preparation of 2,6,7-(or 2,3,7-)trinitrofluorenone by boiling fluorenone with fuming nitric acid. The constitution of the nitro compound was based on the fact that oxidation gave 3,4-dinitrobenzoic acid and that it could be prepared by further nitration of 2,7-dinitrofluorenone. The entrance of the third nitro group into a position ortho to another nitro group is definitely unusual. Also, if the phenylene radical is the directing factor, as stated by Morgan and Thomason, the nitro group would not enter the position assigned to it by Schmidt. The literature revealed that Bell (18) had reported the formation of 2,4,7-trinitrofluorenone, which is identical with Schmidt's compound, by the nitration of 4-nitrofluorenone with concentrated nitric acid. It is seen then that the position of one nitro group (3-) in Schmidt's compound is incorrect on the assumption that no migration of the nitro group took place during the reaction. The formation of the 2,4,7-trinitro compound seems more plausible, in view of the fact that dinitration of fluorene or fluorenone involves the 5-position (positions 4 and 5 being equal).



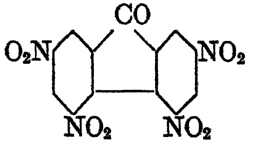
(Bell)





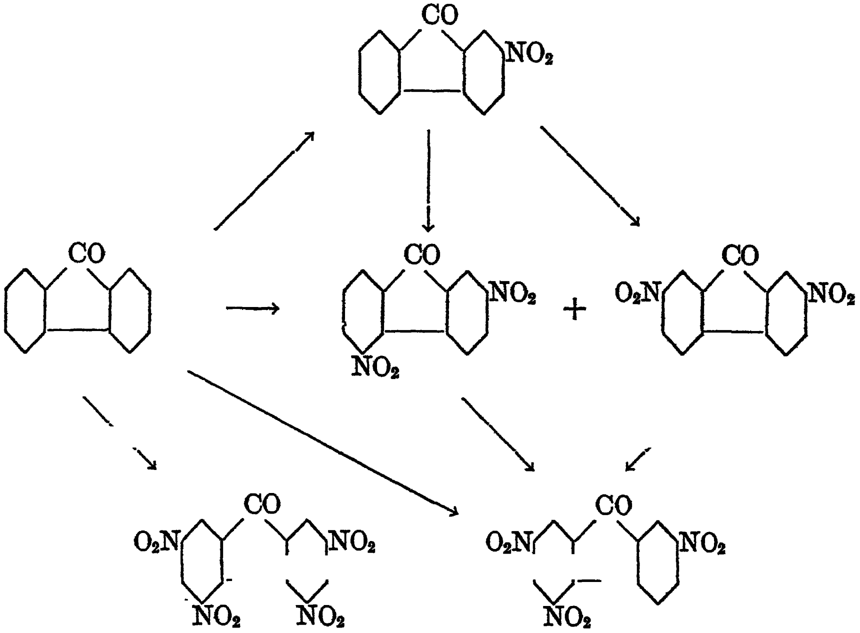
(Schmidt)

Schmidt reported that on boiling fluorenone with concentrated sulfuric acid and red fuming nitric acid 2,3,6,7-tetranitrofluorenone was obtained. It seems more reasonable to us that this compound should prove to be 2,4,5,7-tetranitrofluorenone, for on the introduction of the fourth nitro group into 2,4,7-trinitrofluorenone the 5-position represents the only remaining position which is meta to another nitro group and also ortho to the phenylene radical (the para position being filled).



The validity of Schmidt's results could be easily checked by the dinitration of the known 4,5-dinitrofluorenone. If a compound were obtained identical with Schmidt's 2,3,6,7-tetranitrofluorenone, it would be evident that the positions 3 and 6 are in error.

The following is a tentative scheme for the nitration of fluorenone:



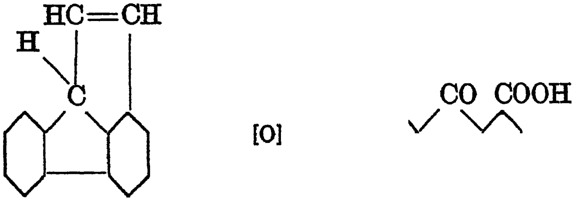
Courtot (53) made a preliminary attempt to determine the orientation of such trisubstituted compounds as X-nitrofluorene-2,7-disulfonic acid and X-nitro-2,7-dibromofluorene, which were prepared by nitrating the respective disubstituted fluorene compounds.

XI. CARBOXYLIC ACIDS

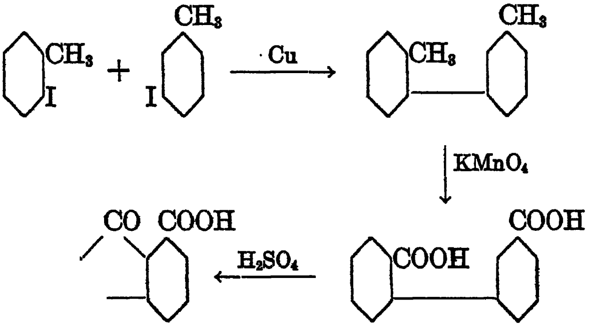
Fluorene-2-carboxylic acid was first prepared by Fortner (107) by the hydrolysis of 2-cyanofluorene, which he obtained from 2-aminofluorene by the Sandmeyer reaction. The silver salt was a white insoluble compound and the methyl ester melted at 120°C. It underwent all the characteristic reactions of an aromatic carboxylic acid. The preparation of fluorene-1-carboxylic acid by Fieser and Seligman (98) in an 84 per cent yield from fluorenone-1-carboxylic acid, using sodium amalgam as the reducing agent, was significant in that it afforded a method of preparing other fluorenecarboxylic acids from the better known fluorenonecarboxylic acids.

Owing to the fact that oxidation is a common method for the preparation of carboxylic acids and that the indirect syntheses also usually lead to fluorenones rather than to fluorenes, we may naturally expect more to be known of the fluorenone acids. All four possible monocarboxylic acids of fluorenone are, therefore, known.

Fluorenone-1-carboxylic acid was prepared easily by the oxidation of fluoranthene with chromic acid (98, 100b, 101, 117, 136). This is the best



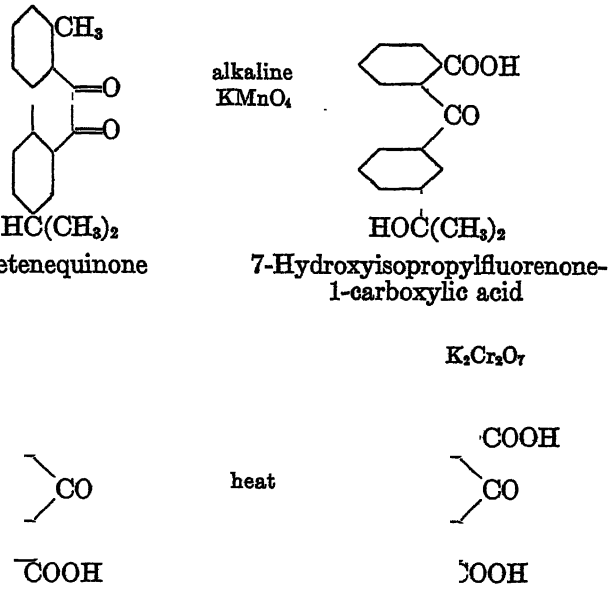
method of preparation; the yield was approximately 50 per cent (98). Mayer and Freitag (194, cf. 284) synthesized it in the following way:



(Cf. 170)

Syntheses of this type are impractical in most cases for preparative purposes, but they are of considerable theoretical importance.

Fluorenone-2-carboxylic acid can be obtained by the oxidation of fluorene-2-carboxylic acid with chromic acid (107), but a more convenient method has been described by Dziewonski and Schnayder (84, cf. 178). 2-Fluoryl methyl ketone, prepared by the action of acetyl chloride on fluorene in the presence of aluminum chloride, on oxidation gave fluorenone-2-carboxylic acid. Hinkel, Ayling, and Beynon (142) prepared it by the oxidation of 2-fluorenealdehyde, which they obtained in 75 per cent yield as a result of one operation on fluorene. The acid was first reported by Bamberger and Hooker (11, cf. 189), who obtained it as a product of the action of heat upon the 1,7-dicarboxylic acid prepared by the oxidation of retenequinone. The following equations illustrate the various products of oxidation:



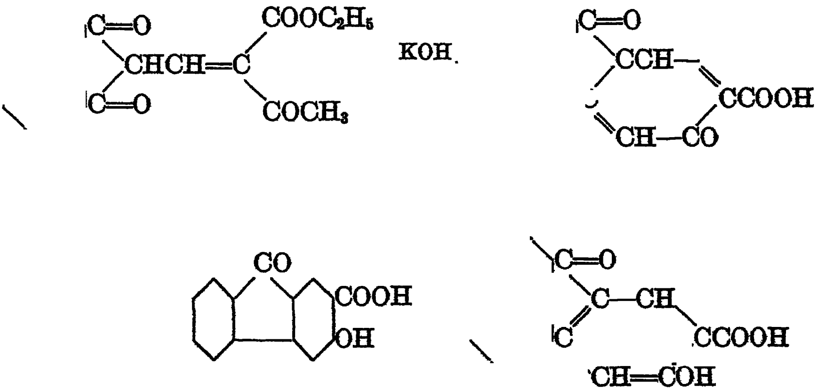
Retenequinone

7-Hydroxyisopropylfluorenone-1-carboxylic acid

Fluorenone-2-carboxylic acid

Fluorenone-1,7-dicarboxylic acid

Errera and La Spada (90) synthesized the 3-hydroxy derivative of fluorenone-2-carboxylic acid by heating ethyl indandionemethenylacetoacetate with an aqueous solution of potassium hydroxide. The reaction probably took place in the following manner.



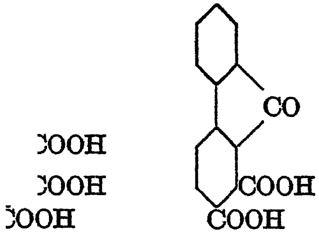
Heating the acid to its melting point (279°C.) caused carbon dioxide to split off, giving 3-hydroxyfluorenone, m.p. 228°C.

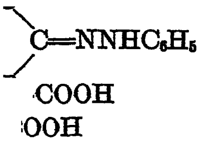
Fluorenone-3-carboxylic acid was prepared by heating 2,3′-diphenic acid with sulfuric acid (287). The reaction was shown to be correct, for the same acid was obtained by oxidizing 3-methylfluorenone with potassium permanganate. It was a yellow crystalline substance, melting at 285°C.

Fluorenone-4-carboxylic acid was the product of the reaction of various reagents upon diphenic acid or diphenic anhydride. It crystallized in yellow needles, melting at 227°C. In its preparation Graebe and Aubin (127) used concentrated sulfuric acid, phosphorus oxychloride, or zinc chloride, while Pick (227) and Gotz (124) used aluminum chloride in benzene or toluene solution. Underwood and Kochman (319) used stannic chloride. Huntress, Herschberg, and Cliff (152) showed that heat caused its conversion to fluorenone.

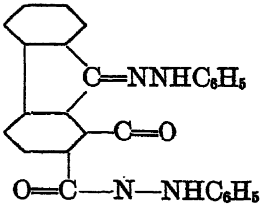
Besides the fluorenone-1,7-dicarboxylic acid already mentioned, several other dicarboxylic acids have been prepared. Von Braun, Manz, and Kratz (34a) have shown that fluoranthene-9-carboxylic acid on oxidation with chromic acid gave a mixture of fluorenone-1,6- and -1,7-dicarboxylic acids; however, if the fluoranthene nucleus were first partially reduced and then oxidized, fluorenone-1,6-dicarboxylic acid was obtained, as shown on page 302.

Fluoranthene-3-carboxylic acid was oxidized to fluorenone-1,2-dicarboxylic acid, which readily formed an anhydride melting at 318–320°C. This same acid has been prepared recently by Charrier and Ghigi (42) by the action of concentrated sulfuric acid on biphenyl-2,3,4-tricarboxylic acid. They gave the melting point of the acid as 330°C. and of the anhydride as 315–320°C., which checked with von Braun's work. Heat caused the loss of carbon dioxide to give fluorenone-2-carboxylic acid. On attempting to prepare the phenylhydrazone of fluorenone-1,2-dicarboxylic acid they obtained two compounds which were formulated as follows:



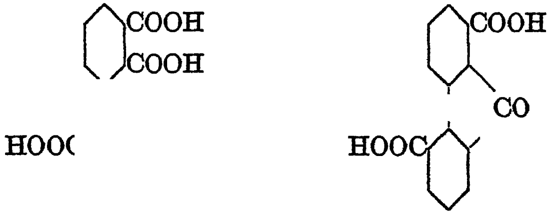


Simple phenylhydrazone



Anilinoimidophenylhydrazone

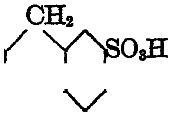
Fluorenone-1,5-dicarboxylic acid was prepared in a similar manner, using biphenyl-2,3,2′-tricarboxylic acid.

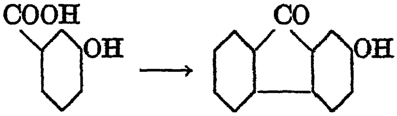


Boiling with quinoline and copper powder caused the removal of the carboxyl group in the 5-position, giving fluorenone-1-carboxylic acid (cf. page 300).

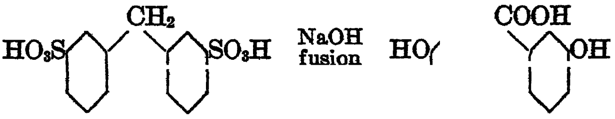
XII. SULFONIC ACIDS

The action of sulfuric acid on fluorene led to substitution in the 2-position and further treatment gave rise to fluorene-2,7-disulfonic acid. Sulfonation in acetic anhydride resulted in an almost quantitative yield of fluorene-2-sulfonic acid (15, 326). Fluorenone-2-sulfonic acid was formed on oxidation. Courtot and Geoffroy (55, 54, cf. 143) used chlorosulfonic acid. These same authors proved by fusion with alkali that the sulfonic acid group entered the 2-position. This treatment opened the five-membered ring. Sulfuric acid, however, reconverted the product to 2-hydroxyfluorenone.





Fluorene-2,7-disulfonic acid was obtained by heating fluorene and concentrated sulfuric acid at about 95°C. (267). Schmidt, who carried out an alkali fusion of this compound, interpreted the compound obtained as 2,7,9,9-tetrahydroxyfluorene; however, Courtot and Geoffroy showed later that the true reaction was as follows:



4,4′-Dihydroxybiphenyl-2-carboxylic acid

Heating the latter compound with zinc chloride gave 2,7-dihydroxyfluorenone; phosphorus pentachloride converted it into 2,7,9,9-tetrachlorofluorene.

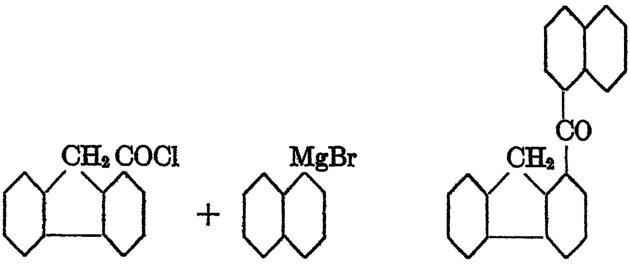
Both fluorene-2-sulfonic acid and fluorene-2,7-disulfonic acid yielded the usual derivatives of an aromatic sulfonic acid; however, as pointed out, alkali fusion did not give the hydroxy compound directly.

Courtot (53) has shown that 2-nitrofluorene when sulfonated gave 2-nitrofluorene-7-sulfonic acid in quantitative yields. 2-Aminofluorene-7-sulfonic acid was obtained on reduction with stannous chloride. The sodium salt of the latter compound gave a remarkably stable diazo compound. Courtot prepared a trisulfonic acid by treating fluorene-2,7-disulfonic acid with oleum, but he was unable to determine the position of the third sulfonic acid group. Solutions of the potassium salt of this compound exhibited in alkaline solution an intense green color which changed to red on acidification.

XIII. KETONES

The majority of fluorene ketones which are known have been prepared by the Friedel–Crafts reaction. Again the 2- and 7-positions were taken up by the entering keto group; however, there is one example of a fluorene-2,3-diketone being formed along with the normal 2,7-isomer. Ketones involving other positions may be synthesized from the acid chloride of the appropriate fluorenecarboxylic acid or fluorenonecarboxylic acid. For example, Gotz (124) synthesized 4-benzoylfluorenone from fluorenone-4-carbonyl chloride and benzene in the presence of aluminum chloride.

Fieser (98) has described another method, using a Grignard reagent and the carbonyl chloride. In this way he synthesized 1-α-naphthoylfluorene in a 56 per cent yield from fluorene-1-carbonyl chloride and α-naphthylmagnesium bromide. This method, of course, cannot be used with fluorenones.

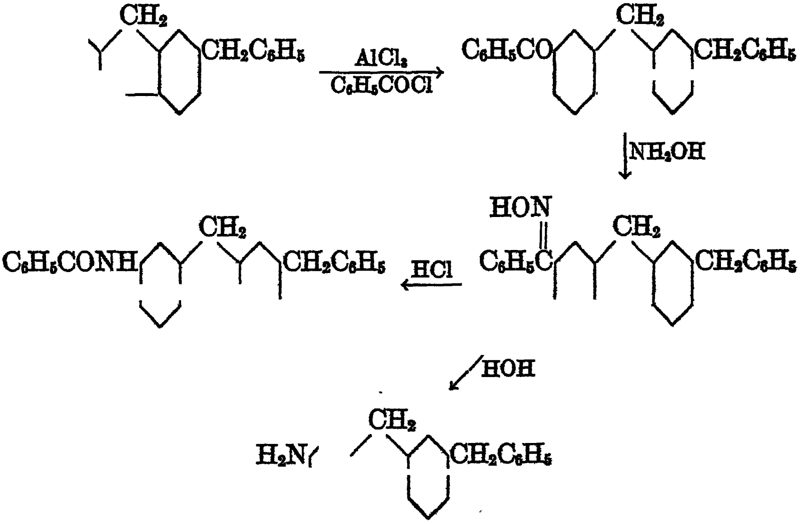


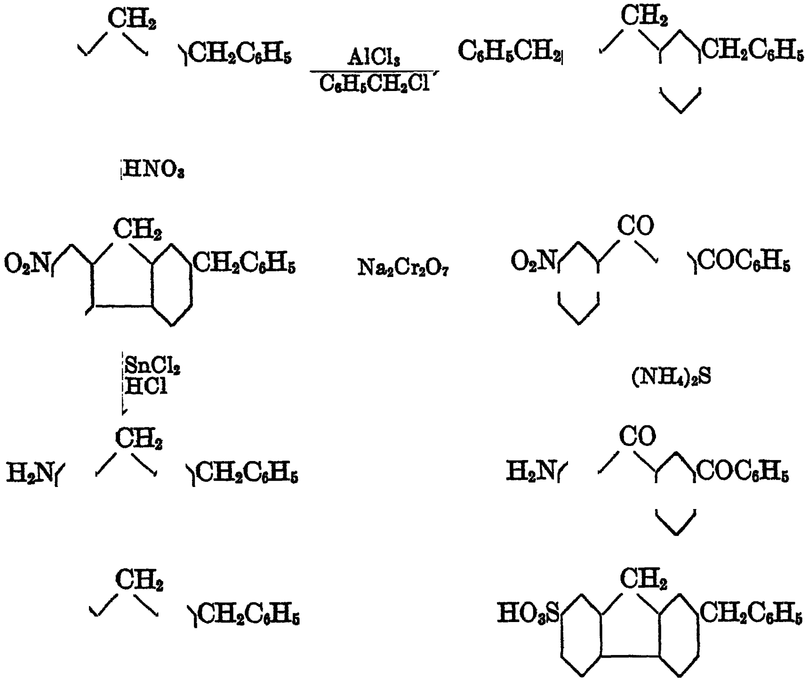
2-Benzoylfluorene (phenyl 2-fluoryl ketone) was prepared by Fortner in 1902 (106, cf. 94) by the action of benzoyl chloride on fluorene in the presence of aluminum chloride in carbon disulfide solution. Perrier's method produces a purer product (238); in 1903 he called attention to his paper presented in 1892 before the Acadèmie des Sciences, Paris, in which he described the preparation of this compound and its oxime (224). Perrier first allowed the benzoyl chloride to react with aluminum chloride and then added the fluorene. The product was insoluble in carbon disulfide and so could be washed free of tar before hydrolysis. Fortner showed that the benzoyl group entered the 2-position by synthesizing 2-benzoylfluorene from 2-aminofluorene. Reduction with zinc dust gave 2-benzylfluorene, a compound previously reported by Goldschmiedt (116), who obtained it from fluorene and benzyl chloride in the presence of zinc dust. Sodium dichromate and acetic acid oxidized 2-benzoylfluorene to 2-benzoylfluorenone.

These compounds have been investigated quite recently by Dziewonski and coworkers. 2,7-Dibenzoylfluorene was prepared from 2-benzoylfluorene by the Friedel–Crafts reaction with heat (82). In proving the constitution of 2,7-dibenzoylfluorene and other similar compounds, Dziewonski made use of the Beckmann rearrangement of the oximes to give derivatives of the known amino compounds. Thus 2,7-dibenzoylfluorene dioxime underwent rearrangement to 2,7-dibenzoylaminofluorene. The latter may be prepared by benzoylating 2,7-diaminofluorene or the benzoyl derivative may be hydrolyzed to 2,7-diaminofluorene (79).

Dziewonski and Reicher (83) also studied the preparation of 2-benzylfluorene by the Friedel–Crafts reaction.

A summary of some of the other reactions carried out by Dziewonski and others is given below.



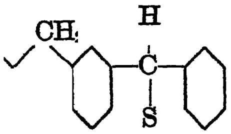


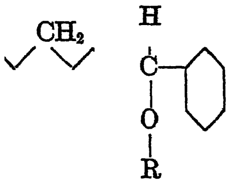
The amino compounds were diazotized and coupled in the standard way with various naphthalene derivatives to give highly colored compounds.

Ray and Pelletier (223) prepared the oxime of 2-benzoylfluorene and reduced it to the amine with sodium amalgam.

Ray and Harrold (137) reduced 2-benzoylfluorene to phenyl-2-fluorylcarbinol. This carbinol was converted into the chloride and the bromide; the iodide was obtained by the reaction of the bromide with methyl iodide (238).

These halides reacted with mercaptans to give a number of sulfides of the general formula I. Alcohols also reacted with these halides to give





II

the corresponding ethers (II).

Ray and Palinchak (240) have prepared 2-benzoyl-9-nitrofluorene and are trying to resolve it by combining it with an optically active substance. The results so far have been unusual.

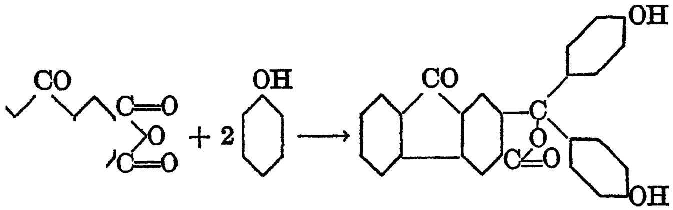
Dziewonski and Schweiger (85) prepared 2-propionylfluorene and 2,7-dipropionylfluorene by the interaction of propionyl chloride, fluorene, and aluminum chloride in carbon disulfide. The constitution of these compounds was established from the oximes, as described previously. 2-Propionylfluorene on oxidation with sodium dichromate and acetic acid gave a mixture of 2-propionylfluorenone and fluorenone-2-carboxylic acid.

The investigation of Dziewonski and Schnayder (84) on the condensation of acetyl chloride with fluorene in the Friedel–Crafts reaction gave results analogous to those obtained with other acid chlorides. 2-Acetylfluorene and 2,7-diacetylfluorene were formed and their constitution established from the oximes.

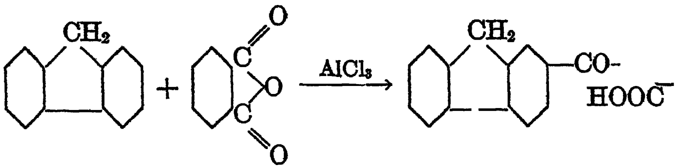
In addition, oxidation of 2-acetylfluorene gave fluorenone-2-carboxylic acid, while vigorous oxidation of 2,7-diacetylfluorene with an excess of sodium dichromate and acetic acid gave fluorenone-2,7-dicarboxylic acid (81).

Dziewonski and Kleszcz (80) investigated the same condensation more carefully, particularly with reference to the temperature at which the reaction was carried out. They found that at 5–10°C. 2-acetylfluorene was the main product; however, at 20–25°C. a mixture of 2,7-diacetylfluorene and an isomeric diacetylfluorene was obtained. When the reaction was carried out at the boiling point of the solvent (carbon disulfide) the isomeric diketone was the main product. The dioxime of the isomer was prepared and on rearrangement yielded a diacetyldiaminofluorene which was easily hydrolyzed to a diaminofluorene. Dziewonski and Kleszcz characterized the isomer as 1,2-diacetylfluorene, because the diaminofluorene that they obtained was identical with the 1,2-diaminofluorene of Diels, Schill, and Tolson (72). Dziewonski and Kleszcz were apparently unaware that Eckert and Langecker (87) had shown in 1928 that Diels' 1,2-diaminofluorene was really 2,3-diaminofluorene. It is then evident that the compound is actually 2,3-diacetylfluorene instead of 1,2-diacetylfluorene; however, it is still incorrectly reported in the literature as 1,2-diacetylfluorene.

2,3-Diacetylfluorene on vigorous oxidation should yield the unknown fluorenone-2,3-dicarboxylic acid. This acid represents the fluorene analog of phthalic acid and should undergo the many interesting reactions of phthalic acid and phthalic anhydride. For example, the anhydride of fluorenone-2,3-dicarboxylic acid should give with phenol and zinc chloride the fluorene analog of phenolphthalein.

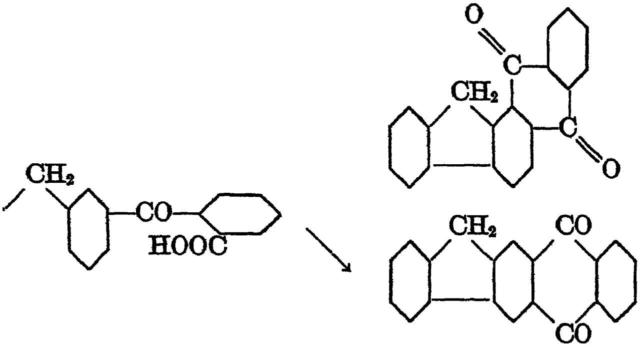


2-Fluoroyl-*o*-benzoic acid has been prepared by the Friedel–Crafts reaction from fluorene and phthalic anhydride (61, 119).



Goldschmiedt and Lipschitz (118, 119) reported two isomeric methyl esters of 2-fluoroyl-*o*-benzoic acid, one melting at 200–202°C. and the other at 126–128°C. They prepared the latter ester without isolation of the intermediate acid chloride; it is possible that the high melting compound was due to the unreacted acid.

When the ethyl ester was heated at 230°C. with potassium hydrogen sulfate, or when the acid alone (61) was heated to 300–320°C., phthalylfluorene was formed; in the latter case the yield was 100 per cent. The ring closure may take place in either the 1- or the 3-position.



Ring closure was shown to take place in the 3-position (17, 215). Koelsch (172) also found the 3-position more reactive than the 1-position, when he studied the cyclization of 2-fluorene-γ-butyric acid.[14] He showed that the 3-position was involved in the ring closure by reducing the ketotetrahydrobenzofluorene to a tetrahydrobenzofluorene which was dehydrogenated with sulfur to 2,3-benzofluorene. Oxidation gave the known 2,3-benzofluorenone (312). Many similar compounds have been prepared (10, 33, 96, 173, 190, 226, 253, 321).

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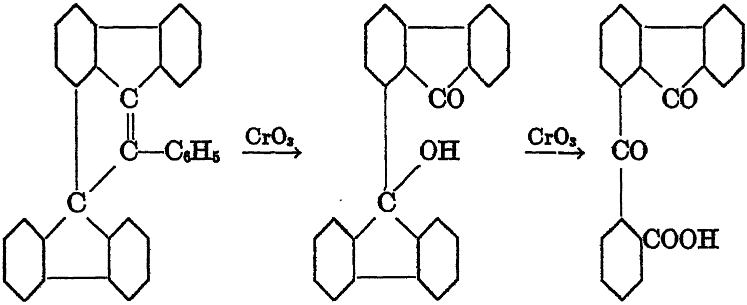
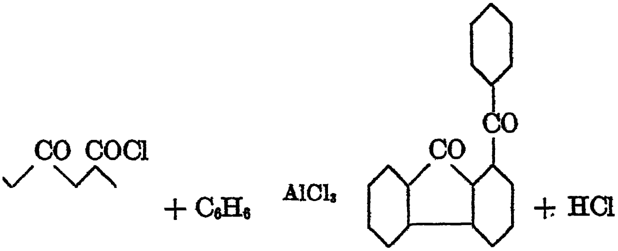
[14] This compound was prepared by condensing succinic anhydride with fluorene in the presence of aluminum chloride and reducing the carbonyl group with zinc amalgam.

2-Fluoroyl-*o*-benzoic acid may be oxidized to the corresponding fluorenone with chromic acid (62, 119). Ray (237) has carried out the reduction of the ketone to the carbinol with zinc and potassium hydroxide. This carbinol should be resolvable, and Ray and Liszniewska (239) have obtained slight indications of its resolution. The ketone group also has been completely reduced to methylene (17, 215).

1-Fluorenonoyl-*o*-benzoic acid [*o*-(fluorenone-1-carbonyl)benzoic acid] was prepared by Koelsch (170) by the degradation of 1-biphenylene-2-phenyl-3,4-phenyleneindene.

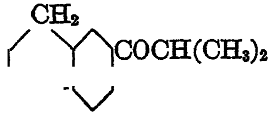


Decarboxylation with cupric carbonate gave 1-benzoylfluorenone. The reaction was checked by a synthesis of the latter compound from fluorenone-1-carboxylic acid.

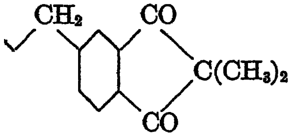


1-Fluorenonoyl-*o*-benzoic acid was found to exist in two interconvertible forms, one yellow and the other orange. By proper crystallization from acetic acid either form could be obtained.

Freund, Fleischer, and Stemmer (108) attempted to prepare fluorene indandiones by condensing dimethylmalonyl chloride with fluorene. Three crystalline compounds were separated from the reaction mixture, one of which was identified as a fluorene isopropyl ketone.



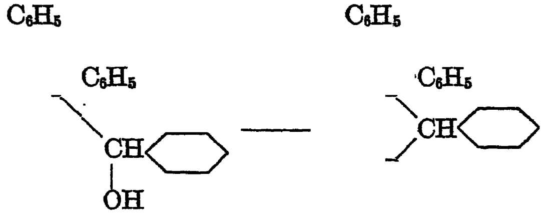
The other two compounds analyzed correctly for fluorenedimethylindandiones, but the authors were unable to determine their structure. One of them probably was 2,3-fluorenedimethylindandione.



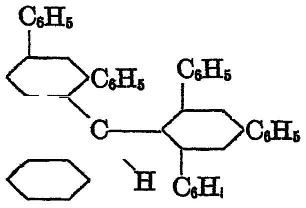
XIV. FLUORENE DERIVATIVES FROM HIGHLY PHENYLATED COMPOUNDS. SPIRO COMPOUNDS

During the last ten years there has been an increasing number of investigations of compounds containing many aromatic rings. Attempts to prepare derivatives of these compounds, especially when carbinols were converted to halides, frequently brought about a transformation to fluorene derivatives which seemed to represent a more stable system.

Kohler and Blanchard (174) described several examples. Triphenylbenzohydrol was transformed into 1,3,9-triphenylfluorene when it was treated with a halogen acid.

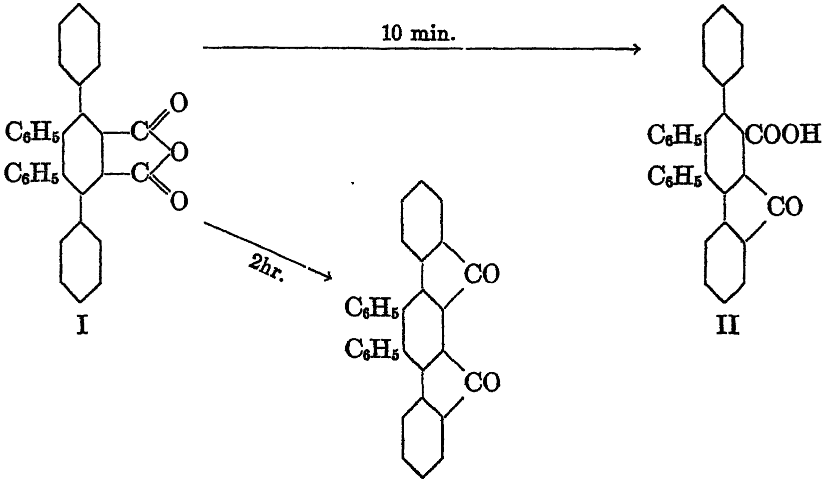


Similarly hexaphenylbenzohydrol gave 1,3-diphenyl-9-triphenylphenylfluorene.



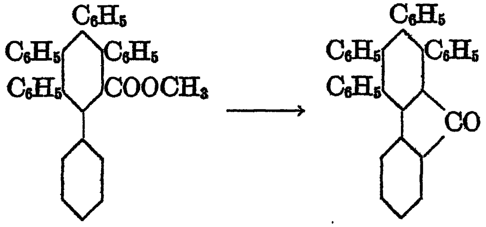
On attempting to prepare the acid chloride of triphenylbenzoic acid, they obtained 1,3-diphenylfluorenone. The latter compound when treated with phenylmagnesium bromide gave 1,3,9-triphenylfluorenol.

Dilthey, Thewalt, and Trösken (74) synthesized several unusual fluorene compounds from polyphenylbenzenes. On heating tetraphenylphthalic anhydride (I) in benzene in the presence of aluminum chloride for 10 min. a reaction occurred which gave 2,3,4-triphenylfluorenone-1-carboxylic acid (II). When the mixture was boiled for 2 hr. they obtained a compound which they called diphenyldifluorenone (III).

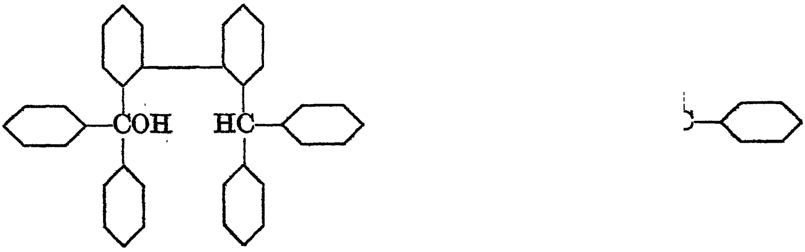


III

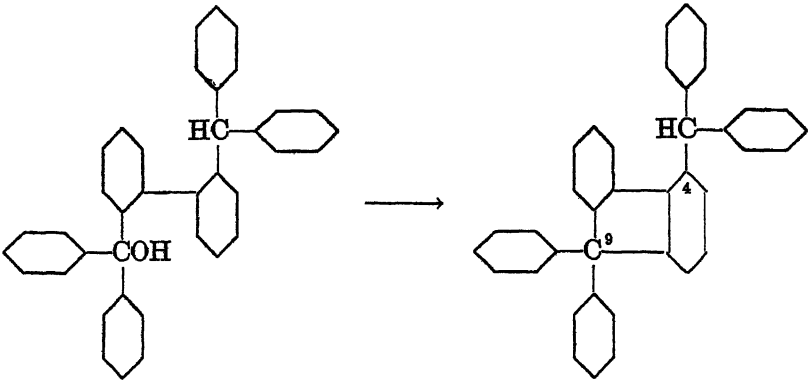
1,2,3,4-Tetraphenylfluorenone was prepared by heating the methyl ester of pentaphenylbenzoic acid in benzene solution with either aluminum chloride or phosphorus oxychloride.



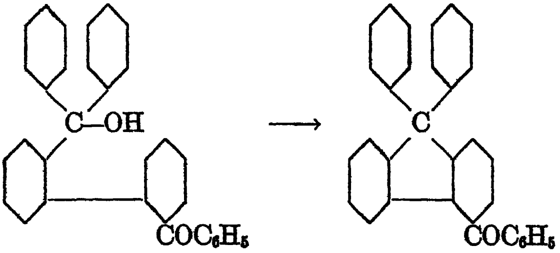
Sergeev (281) in his investigations of polyphenyl derivatives of *o,o'*-ditolyl attempted to carry out the following synthesis:

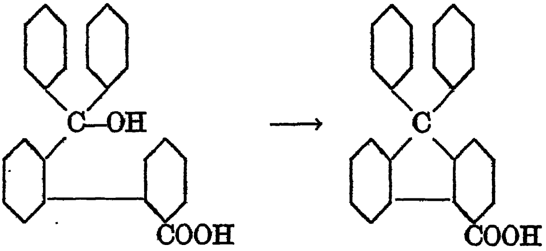


However, all attempts to split off water resulted in 100 per cent yields of 4-benzohydryl-9,9-diphenylfluorene.



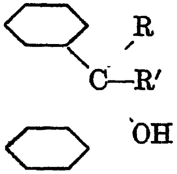
Two other instances of this type of transformation were encountered by Sergeev, as shown in the following equations:

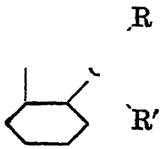




The first reaction took place under the influence of acidic reagents; the second resulted when he attempted to replace the hydroxyl group with halogen.

This type of ring closure to form fluorene derivatives seems always to occur in carbinols in which one valency is linked to an aromatic ring, which in turn has another phenyl group ortho to the carbinol group. In other words, we may expect fluorene compounds from carbinols of the following type.[15]

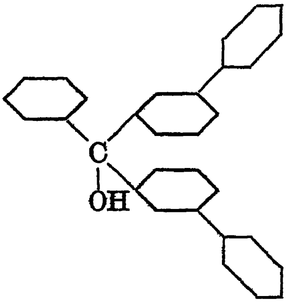


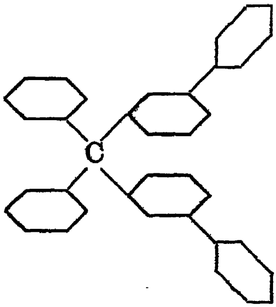


There is additional experimental evidence to justify this statement. Ullmann and von Wurstemberger (318) obtained 9,9-diphenylfluorene by heating crude 2-phenyltriphenylcarbinol with sulfuric acid (R and R′ = Ph). Khotinsky and Patzewitch (160) obtained the same results, using acetic acid to bring about the ring closure. A synthesis of 9-phenylfluorene in quantitative yields from *o*-phenylbenzohydrol has been described by Koelsch (173). Boiling the carbinol in acetic acid containing a little sulfuric acid caused ring closure.

Clarkson and Gomberg (46) succeeded in preparing 2-phenyltriphenylcarbinol in the pure crystalline state, but repeated attempts to prepare the chloride always resulted in the formation of 9,9-diphenylfluorene. Further investigation concerning the conditions under which ring closure took place showed that even very mild treatment was sufficient.

9,9-Di(3-biphenyl)fluorene was formed from 2,3′,3″-triphenyltriphenylcarbinol when a small amount of acid was added.





Clarkson and Gomberg then prepared 9-(2-biphenyl)-9-fluorenol, expecting a greater stability and consequent successful preparation of the chloride. The fluorenol was unchanged by recrystallization from acetic acid, but on the addition of *one drop* of hydrochloric acid ring closure took place. It can be seen that by this ring closure a compound is formed in

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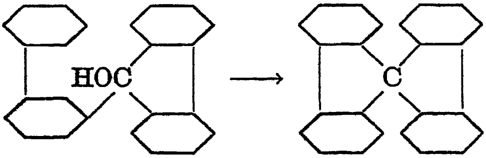
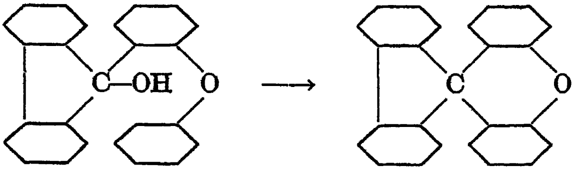
[15] If the linkage between the two phenyl radicals contained a carbon atom or an oxygen atom, ring closure should give rise to anthracene derivatives or xanthenes, respectively.



I

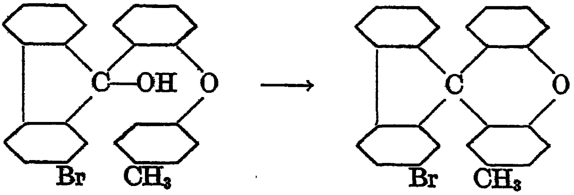
which one carbon atom is common to two rings. Compounds of this type are called spiro compounds, or, more simply, spirans. 9,9-Spirobifluorene (I) is unusual in that it is the simplest representative compound possible in which all four valencies of the spiro carbon atom are linked to purely aromatic groups.

Clarkson and Gomberg by this method prepared a series of interesting spirans, some of which are shown in the following equations.



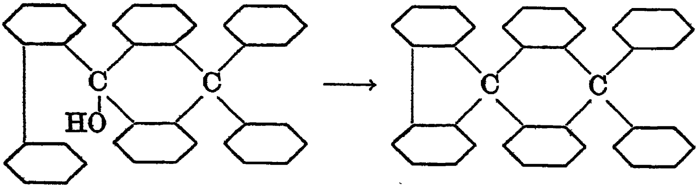
9-(2-Phenoxyphenyl)-9-fluorenol

Spiro-9-fluorene-9′-xanthene



9-(2-Phenyl-*p*-tolyl ether)-2-bromo-9-fluorenol

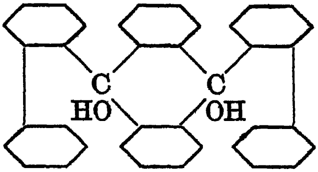
Spiro-9-(2-bromofluorene)-9′-(2′-methylxanthene)



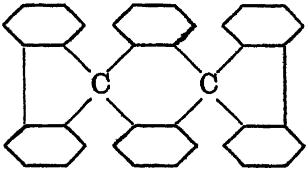
9-(2-Biphenyl)-10,10-diphenyl-9,10-dihydro-9-anthranol

Spiro-9-fluorene-9′-(10,10-diphenyl)-9,10-dihydroanthracene

The next logical step was the preparation of a dispiro compound involving the closure of two rings. It was accomplished as shown in the following equation:



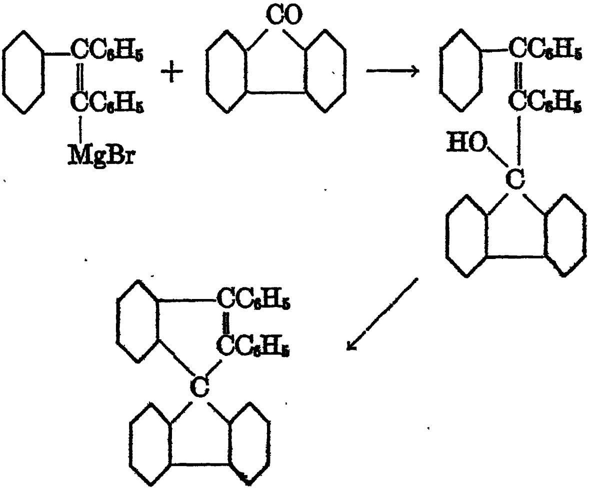
9,10-Di(2-biphenyl)anthraquinol



Dispiro-9,9′-difluorene-(9,10-dihydroanthracene)

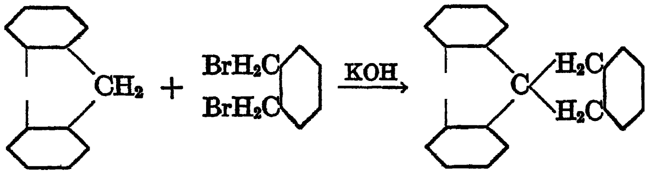
In all these reactions the ring closure was effected by seeming catalytic action of mild dehydrating agents. The yields in most cases were quantitative. All the complex spirans were nicely crystalline, colorless, and very insoluble in the usual organic reagents.

Koelsch (169) reported a spiro compound which he obtained similarly. α-Diphenylene-β,γ,γ-triphenylallyl alcohol, obtained from triphenylvinylmagnesium bromide and fluorenone, on treatment with an acidic reagent formed 1-biphenylene-2,3-diphenylindene.



1-Biphenylene-2,3-diphenylindene

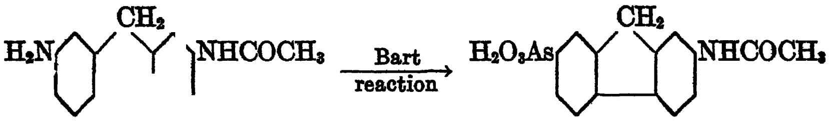
A spiro compound has been prepared directly from fluorene. Fluorene and *o*-xylylene dibromide heated in the presence of potassium hydroxide gave xylylenefluorene (92).



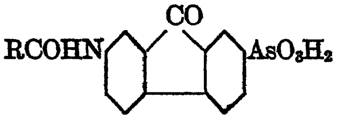
XV. ARSENIC AND PHOSPHORUS COMPOUNDS OF FLUORENE[16]

Arsenic compounds of fluorene have been prepared by two groups of investigators, Cislak and Hamilton in America and Morgan and Stewart in England. Cislak and Hamilton, however, were the first to publish their results. The investigations of Morgan and Stewart were more thorough.

Cislak and Hamilton (45), in an attempt to find new arsenicals which might be of value in chemotherapy, prepared 2-arsonofluorene, 2-arsonofluorenone, and 2-acetylamino-7-arsonofluorene. The following equation illustrates the preparation of the latter derivative.



Morgan and Stewart (207) found that "trypanocidal potency is manifested when an arsenic radical was introduced into fluorenone in conjunction with an amino group." Compounds of the following types were prepared and their therapeutic value determined.



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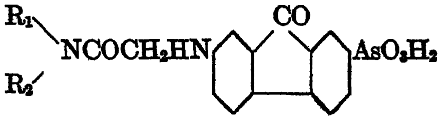

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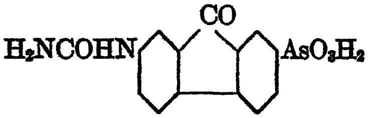

III

The sodium salt of 7-acetylaminofluorenone-2-arsonic acid (type I) was found to be the most efficacious, having an M.L.D.[17] of 15 and an M.C.D. of 10. The conclusion from the work was "that a curative power is manifested when R equals H, reaches a maximum when R is CH_3, and then decreases rapidly until it disappears when R is C_6H_5. Derivatives of type II have little therapeutic value." 7-Carbamidofluorenone-2-arsonic acid (III) had an M.L.D. of 30 and an M.C.D. of 15.

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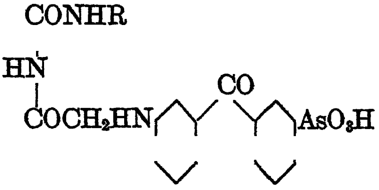
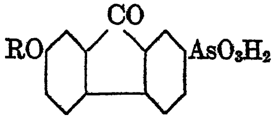
[16] For mercury compounds see page 343.

[17] M.L.D. and M.C.D. are the minimum lethal dose and the minimum curative dose, respectively, in milligrams per 20 g. of mouse.

Morgan and Stewart (208) continued their work and investigated the trypanocidal action of compounds in which the length of the side chain had been increased to form ureides (IV). These compounds were of little value.



IV



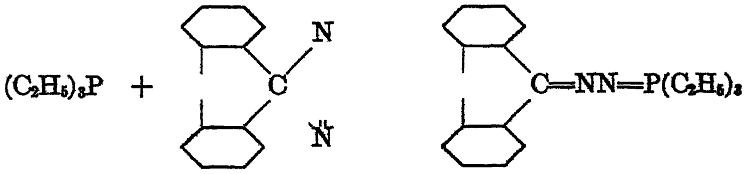
A compound of type V, 7-carbamylmethoxyfluorenone-2-arsonic acid (R being CH_2CONH_2), however, was very effective, having an M.L.D. of 30 and an M.C.D. of 10.

Using 7-aminofluorenol-2-arsonic acid as a starting material they prepared a number of derivatives. One compound of the fluorenol type, 7-glycineamidofluorenol-2-arsonic acid, was curative in doses which did not exceed one-half the minimum lethal dose.

If we regard the 2,7-positions to be in an extended para relationship we find that Benda's observation (20), "that all but a few of the corresponding trypanocidal drugs have nitrogen in para combination with the arsenic," is applicable.

Whether or not these compounds will be of value in the treatment of sleeping sickness cannot be said, but the results obtained thus far seem to indicate a very good beginning.

Phosphorus compounds of the phosphazine type have been prepared by Staudinger and Meyer (297, 298) from diazofluorene and phosphine derivatives. The following equation illustrates their formation:



Triphenylphosphinefluorenoneazine and phenyldiethylphosphinefluorenoneazine were also prepared. On heating, all decomposed with the evolution of nitrogen.

XVI. FLUORENE DYES

Although a large number of fluorene dyes have been prepared, no commercial use of them has apparently yet been made. Sircar and Bhattacharyya (288) have synthesized tetrazo derivatives of 2,7-diaminofluorenone by coupling with various intermediates. Dyes similar to those obtained from benzidine were naturally expected. Table 6 gives the intermediate and the color of the tetrazo compound. All these dyes except Nos. 5, 6, and 12 were substantive to cotton. These same authors also prepared a series of azo dyes from 2-aminofluorenone (288).

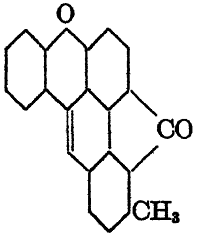
Novelli (220) prepared the bisazo derivative of 2,3,6-naphtholdisulfonic acid and 2,7-diaminofluorene. The sodium salt (4 Na) was a dark violet substance and dyed wool and silk directly. The sodium salt (6 Na) was red and a direct dye for cotton. Other dyes were prepared using H- and K-acids. The study of possible trypanocidal action of these compounds was to be undertaken.

TABLE 6

Fluorene dyes

NO.	INTERMEDIATE	COLOR
1	Phenol	Deep brown
2	*m*-Cresol	Dark brown
3	*o*-Hydroxybenzoic acid	Deep brown
4	β-Naphthol	Deep brown
5	2-Hydroxy-3-naphthoic acid	Brownish violet
6	1-Aminonaphthalene-4-sulfonic acid	Deep reddish brown
7	2,3,6-Naphtholdisulfonic acid	Reddish violet
8	2,6,8-Naphtholdisulfonic acid	Deep brown
9	1-Aminonaphthalene-5-sulfonic acid	Deep brown
10	1-Hydroxy-8-aminonaphthalene-3,6-disulfonic acid	Deep brown
11	1,8-Dihydroxynaphthalene-3,6-disulfonic acid	Bluish violet
12	Dimethylaniline	Deep brown

Sachs and Öholm (251) prepared a vat dye from fluorene and 1,2-naphthoquinone-4-sulfonic acid which gave a variety of mordanted colors. Schaarschmidt and Herzenberg (256) prepared several vat dyes of fluorene which were similar in structure to those of anthraquinone and phenanthraquinone. For example, methylphenanthroanthraquinonefluorenone



was a brown vat dye. Anthraquinone-2,1-fluorenone (254) was an intense red vat dye.

Mukherjee and Dutt (212) condensed aromatic amines and hydroxy compounds with fluorenone to give dibiphenylenexanthenes which were similar in properties to phthalein dyes.

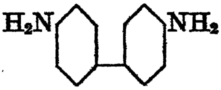
The dyes derived from 2,7-diaminofluorene and 2,7-diaminofluorenone seem to have possibilities in industry, but the present cost of these amines is quite high. Fluorene, nevertheless, is readily available in commercial quantities when the industrial world requires it.

XVII. FLUORENE AND 2,7-DIAMINOFLUORENE IN ANALYTICAL CHEMISTRY

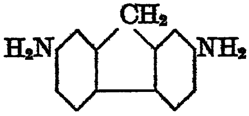
Ditz (75) was the first to report an analytical use for fluorene. He noticed that on the addition of a weak solution of formaldehyde to a solution of fluorene in concentrated sulfuric acid a blue color was formed. Attempts to estimate formaldehyde in milk by this method were unsuccessful, because the test was not sufficiently sensitive for minute amounts of formaldehyde.

Guglialmelli and Delmon (132) studied the color reactions produced by fluorene and concentrated sulfuric acid with various carbohydrates. The test was carried out by adding sulfuric acid to a mixture of 0.5 cc. of an alcoholic solution or suspension of the carbohydrate and 2 to 3 drops of a 2 per cent solution of fluorene in alcohol. Under these conditions carbohydrates which produce furfural when treated with sulfuric acid gave an intense color varying from red to indigo-violet. The colors obtained with glucose, sucrose, α-methylglucoside, and especially with arabinose were very characteristic, and the test may be used for the differentiation of these sugars. DeFazi (67) later extended this test for detecting traces of various aldehydes.

It is evident from the formulas that 2,7-diaminofluorene is very similar in structure to benzidine. Pregl (235) considered it more effective than benzidine in spot tests.



Benzidine



2,7-Diaminofluorene

Guglialmelli and Ruiz (134) found that 2,7-diaminofluorene hydrochloride may replace benzidine in the precipitation of soluble salts of sulfuric, tungstic, molybdic, and chromic acids. It also precipitates meta- and para-tungstates; this is an appreciable advantage over benzidine, since a part of tungstic acid in acid media is converted into meta-, para- and poly-tungstates, which are more or less soluble and would escape precipitation by benzidine. A quantitative procedure for tungsten has been described by these authors. It was also reported that ferro- and ferricyanides and very slight traces of chlorine in water could be detected by this reagent. Nino and Calvet (218) worked out a method for the quantitative determination of zinc, using the diamine as the precipitating agent.

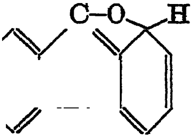
Further studies of the analytical use of 2,7-diaminofluorene were carried out by Schmidt and his coworkers. Schmidt and Hinderer (263, cf. 105) used it to detect small amounts of zinc, cadmium, and copper. 2,7-Diaminofluorene is claimed to possess distinct advantages over benzidine in the detection of peroxidases and persulfates (262, 264). Potassium persulfate can be detected with certainty in dilutions of 1:1,000,000. Since 2,7-diaminofluorene hydrochloride is very sensitive to peroxidases, it may be used to detect blood and to differentiate between boiled and fresh milk. One drop of blood in 50,000 cc. of water gives a distinct blue color; benzidine gives no color at all at this concentration. Schmidt and Hinderer also showed that 0.0_617 g. of chlorine per cubic centimeter of water could be detected with 2,7-diaminofluorene, whereas with benzidine, chlorine can be detected with certainty only in about three times this concentration. 2,7-Diaminofluorene hydrochloride possessed the distinct advantage of being easily soluble in water. The isomer, 2,5-diaminofluorene, was also investigated.

XVIII. STEREOCHEMISTRY OF FLUORENE

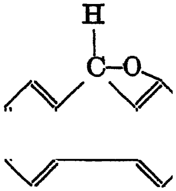
In the course of our description of the chemistry of fluorene we have commented on the claims of various investigators that they had isolated isomers whose existence was not accounted for by the conventional planar formula for the molecule.

Carnelly (38, cf. section III) reported that he had isolated an isomeric form of fluorene itself. This has never been confirmed. The tendency for fluorene to form complexes with other compounds probably explains his results.

Kerp (cf. page 292) reported a red isomeric form of fluorenone to which he assigned the formula



or



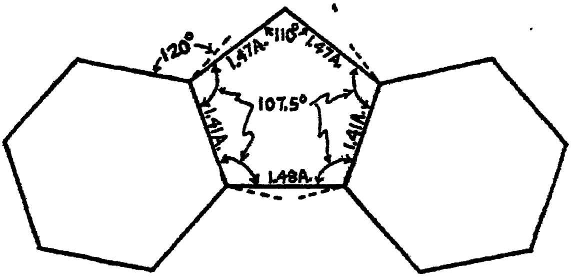
Although Stobbe apparently confirmed the existence of this red isomer, it would seem profitable to reinvestigate it in the light of present knowledge.

The existence of isomeric 9-amino compounds (cf. section VIII C) has not been substantiated by recent exhaustive investigations. Of the two 9-carboxylic acids of Schlenk and Bergmann (cf. section VIII D) the lower melting form probably resulted from imperfect crystals, according to the recent work of Jeanes and Adams (157). These authors found that slow crystallization gave harder and brighter crystals which melted at 232°C. with slight decomposition. Rapid crystallization gave the lower melting (226°C.) form.

Pfeiffer and Lübbe (225) showed that Schlenk and Bergmann's supposed isomeric 9-benzoylfluorene was in reality 9,9-dibenzoylfluorene.

But even though the existence of all cases of stereoisomerides so far reported has been rendered doubtful, the question is by no means disposed of.

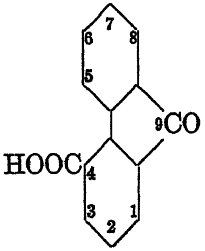
From a consideration of valency angles and interatomic distances a model is produced that would result in considerable strain if a planar formula is assumed (231).

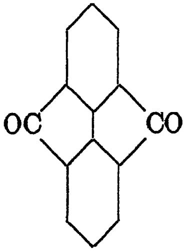


The evidence obtained in x-ray examinations of fluorene might be expected to distinguish between planar and non-planar formulas. But here again the results are open to various interpretations. Stuart (305) has interpreted the data of Hengstenberg and Mark (139) as evidence for the planar configuration. . Dipole moments reported by Hughes, Lefevre, and Lefevre (147) also seem to support this view. Cook and Iball (49) do not agree with these views and maintain that their data are best satisfied by a non-planar formula with each benzene ring inclined 20° to the five-membered ring and 40° to each other. They do not go so far as to postulate isomers, since they suggest that "it may be that the molecule possesses sufficient elasticity to undergo oscillation between two non-planar forms."

The tendency of the five-membered fluorene ring to expand during the Stieglitz rearrangement has been described (cf. page 327). This seems to be evidence of considerable strain, which would imply a planar configuration. In section XIV, however, the formation of spirofluorene compounds seems to represent a more stable ring system. This would imply little strain in the fluorene molecule.

Miller, Parker, and Tomlinson (202) point out that fluorenone-4-carboxylic acid (I) does not undergo further condensation to a compound of the type II.

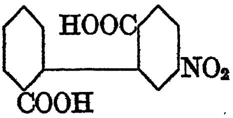




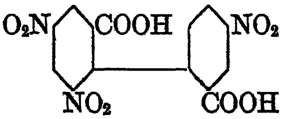
II

This they advance as evidence for the non-planar formula. It seems to us, on the contrary, to indicate that the bond joining the benzene rings is bent, *increasing* the distance between the 4- and 5-positions, which is to be expected if the compound has a planar formula.

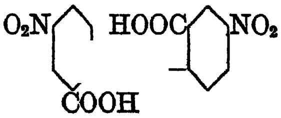
Somewhat more convincing is the work of Bell and Robinson (19). They found that although 5-nitrodiphenic acid (III) gave a fluorenone on heating with sulfuric acid, 4,4′,6′-trinitrodiphenic acid (IV) did not.



III

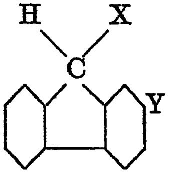


IV



Now, by resolution into its optical antipodes, it has been shown that the two benzene rings of IV are not coplanar. The failure of this compound to form a fluorenone would seem to suggest that fluorenone requires coplanar rings. Any reasoning, however, that is built on the failure of a compound to react is fraught with uncertainty. The explanation might well be that the right conditions were not used. Especially is this the case here, because Underwood and Kochmann (320) have also reported that 4,4′-dinitrodiphenic acid (V) does not give a fluorenone. If this is correct it points to a possible electrochemical effect rather than to steric hindrance.

Of course the resolution of a monosubstituted fluorene compound would be conclusive evidence for the non-planar form. But even such expected antipodes as



have resisted all efforts at resolution (22). This failure of the diastereoisomeric salts to separate, even in what should be classical cases, makes the possibility of resolving non-planar forms remote.

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THE SURFACE ACTIVITY OF PROTEINS

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The authors have set themselves the task of reviewing the literature dealing with the surface activity of proteins. In such a review the subject of protein surface films must occupy a central position. To facilitate the presentation of this material, the subject has been divided into two parts. The first part deals with the surface films of proteins formed spontaneously on protein solutions; the second part describes the work done on protein films spread on pure buffer solutions or on pure water. While there is a marked similarity between these two types of films, they are by no means identical.

During recent years there has been a vigorous revival of interest in the subject of surface films in general and protein films in particular. Much of the new work was anticipated, at least in a semi-quantitative way, many years ago, and due credit should be given these early investigators.

I. Surface Films on Protein Solutions

In 1873 Plateau (126) studied, by means of the retardation of the swing of a magnetic needle floating on the surface, the surface viscosity of protein solutions. Even before this time Melsen (106) and Smee (138) showed independently that an insoluble coagulum of protein was formed when protein solutions were shaken. Ramsden (129) in 1894 described experiments in which he was able to coagulate a number of proteins by shaking their solutions. He showed, for example, that egg albumin, egg globulin, vitellin, serum albumin, serum globulin, fibrinogen, lactalbumin, myosinogen, and potato protein all formed insoluble precipitates or coagula when their solutions were shaken. He definitely suggested that the coagula were due to the rolling or heaping up of the protein film at the air-solution surface. He was also able to show that the process was independent of the nature of the gas present.

From the first there seemed to be an appreciation of the importance of such films to the study of biology. In 1840 Ascherson (6) remarked that oil droplets suspended in albumin solutions had a tough skin or film formed spontaneously around them and suggested such droplets as models for living cells.

In recent years du Noüy (37), followed by several other workers (29, 71), has studied the surface tension of dilute solutions of proteins and attempted to interpret the results in terms of the thickness of the film formed on the protein solution surface. Briefly, these workers claimed to have observed certain very sharp minima in the surface tension of such solutions at certain protein concentrations. They assumed that these minima corresponded to a particular orientation of the protein molecules at the surface. They made the further assumption that all of the protein had been adsorbed at the air–solution surface and glass–solution interface and, further, that the same amount of protein had been adsorbed per unit area on the protein solution–air surface as at the protein solution–glass interface. They then calculated the thickness of the adsorbed film at the various minima in the surface tension–protein concentration curve. From this thickness they calculated the dimensions of the protein molecule. Such measurements and calculations are to be regarded with extreme skepticism. In the first place, it is very doubtful that the minima in the concentration–surface tension curve have a real existence (to be discussed under the section on surface tension), and, secondly, it is very questionable whether the protein is completely adsorbed at the surfaces. Experiments on protein adsorption show that it follows a Langmuir adsorption isotherm (73, 100), and under such circumstances part of the protein would remain in solution. A third difficulty is that with such dilute solutions of protein as were used in these experiments it is almost impossible to know the true protein concentration with any accuracy. A large fraction of the small amount of protein present may have been lost by adsorption on glassware during the preliminary manipulation; also, part of the protein could be lost through surface denaturation. And, lastly, there is no good reason to believe that the minima which were claimed corresponded in any way to orientation on the surface. Certainly the dimensions reported have not been confirmed by the spreading of protein on a buffer solution and measuring the force–area relations of the films.

Wu and Ling (144), following the lead of Ramsden, investigated in a quantitative fashion the coagulation of purified egg albumin, oxyhemoglobin, and methemoglobin brought about by the shaking of solutions of these proteins in glass bottles in a shaking machine. They found, in general, the rate of surface coagulation to be independent of time and concentration but strongly influenced by the rate of shaking and by the size of the bottles. A reaction whose rate is independent of time and concentration is classed as an apparent zero-order reaction and is characteristic of reactions taking place at a surface saturated with reacting materials. It is to be anticipated that, if the protein concentration becomes too low or the rate of creation and destruction of surface too fast, the reaction would fail to follow a zero order. Bull (19) was able to demonstrate that such was the case. Wu and Ling reported the rate of surface coagulation to be greatly influenced by the hydrogen-ion concentration, the maximum rate for egg albumin being at the isoelectric point and nearly independent of salt concentration. Oxyhemoglobin showed a much more complicated behavior in respect both to hydrogen-ion concentration and to salts. The rate of surface coagulation for this protein showed two maxima,—one at pH 3.9 and the other at pH 6.9. The addition of salt (1 per cent sodium chloride) greatly increased the rate of coagulation and shifted the maximum rates to pH 5.0 and 8.7, respectively. The behavior of methemoglobin, as far as it was investigated, was similar to that of oxyhemoglobin, but the rate of coagulation was somewhat slower. Wu and Ling studied the influence of surface-active materials and showed that alcohol, ether, and saponin greatly diminished the rate of surface coagulation of both methemoglobin and egg albumin. They also reported that the pH values of unbuffered solutions of egg albumin and oxyhemoglobin changed upon shaking. They determined the rate of surface coagulation of egg albumin at 25°C. and 38°C. and reported a Q_{10} over this temperature range of 1.09. Incidentally, they were unable to confirm Hopkins' (74) earlier observation that sulfur is given off as hydrogen sulfide or as some other volatile sulfide when egg albumin solutions are shaken.

Neurath and Bull (119) studied the density of surface-coagulated egg albumin and its water-binding capacity. They found its density to be 1.3016, using xylene in the pyknometer as the displacing liquid. This is a higher density than that of the heat-coagulated egg albumin (1.2940) and considerably greater than that for the native egg albumin (1.2655). They estimated the water binding (hydration) of surface-coagulated egg albumin to be from 0.19 to 0.20 g. of water per gram of protein. Bull (21) determined the density of native, surface-coagulated, and heat-coagulated egg albumin, using hydrogen as a displacing gas, and found that all three forms of this protein had, within experimental error, the same density, which was 1.345 ± 0.005. The different densities reported by Neurath and Bull, using xylene as the displacing liquid, can probably be attributed to lack of penetration of this liquid into the protein.

Bull and Neurath (23), unaware of the work of Wu and Ling described above, investigated the surface denaturation and coagulation of egg albumin produced by shaking solutions of this protein in glass bottles. They confirmed the results of Wu and Ling on most points, but were unable to agree with the Chinese workers that surface coagulation cannot be separated into two steps in analogy to heat coagulation: namely, (*1*) the production of soluble surface-denatured protein and (*2*) the coagulation of this soluble surface-denatured protein. Bull and Neurath found that away from the isoelectric point, both on the acid and on the alkaline side, a large fraction of the surface-denatured protein was soluble, as evidenced by the fact that, if such solutions are brought to the isoelectric point, a precipitation of the surface-denatured but uncoagulated protein takes place. Wu and Wang (145) challenged Bull and Neurath on this point, but were unable to offer a reason for the disagreement. Bull and Neurath (24) repeated their own experiments and confirmed their previous findings. The reviewers feel that a positive result in this connection is of more significance than a negative one.

Bull and Neurath also investigated the influence of gelatin on the surface coagulation of egg albumin and found that this substance was without effect up to its gelling point. They also studied the change of pH experienced by unbuffered protein solutions upon surface denaturation in some detail and pointed out the close analogy with the behavior of heat-denatured egg albumin solutions in this regard.

Bull (21) determined the rate of surface coagulation of egg albumin solutions at 45°C. and 25°C., and found a Q_{10} over this temperature range of 0.95, which is somewhat less than that reported by Wu and Ling. In any case, however, the temperature coefficient of surface coagulation is very much less than that of heat coagulation and is more in line with that found for urea denaturation of egg albumin (75).

Bull (19) developed an apparatus for the study of protein films on protein solutions which yielded somewhat more quantitative results than it was possible to attain by the bottle-shaking technique. He employed a roller of known dimensions dipping into an egg albumin solution and rotated at known speeds. With this technique it is possible to know accurately the rate and extent of creation and destruction of air–protein solution surface. Then from a knowledge of the amount of surface-coagulated protein in a given time may be calculated the amount of surface-coagulated protein per unit of surface area as a function of speed of rotation and of protein concentration. From a knowledge of the specific volume of the protein, the thickness of the film of denatured protein at the surface is calculated. It was found that the thickness of the film calculated in this manner was a smooth function of the speed of rotation of the drum; this allowed an extrapolation of the thickness of the film to zero speed of rotation to yield an approximate estimate of the thickness of the film on a quiescent solution at the various protein concentrations used. The results of such an extrapolation indicate a rather complicated picture for the surface film on a quiescent protein solution. As far as can be judged, a layer of denatured egg albumin molecules is immediately on the surface and is about 10 Å. in thickness. Such a film would correspond to a strongly compressed spread film produced by dropping a small amount of dilute protein solution on a pure buffer solution (the properties of such films are to be described in a later section) and involves, as Neurath (115) has suggested, an unfolding of the native molecules at the surface to produce the denatured protein. Under this denatured film is adsorbed a layer of more or less spherical, native molecules which is about 40 Å. thick. The extent of adsorption of this second layer is dependent on concentration, and either does not exist below a concentration of 0.10 per cent protein or else forms relatively slowly so as to be missed by the roller technique, which allows as a maximum only 3 sec. for the formation of the film. An important point brought out in this research is the remarkable rapidity of formation of the surface film. For example, at concentrations greater than 1.0 per cent, the two-layer film is complete in less than 0.7 sec. after creation of the new surface. If the protein concentration is sufficiently great and the rate of creation and destruction of solution surface is not too high, the surface will be completely saturated with protein and the limiting factor in the production of denatured protein is the rate of creation of new surface; accordingly the reaction has the kinetics of that of a reaction of an apparent zero order.

SURFACE TENSION OF PROTEIN SOLUTIONS

It appears that in most cases there is no true equilibrium established between the protein solution and the surface film. Langmuir (98) has emphasized the tremendous insolubility of spread films of proteins and the improbability of any of the protein molecules leaving the surface and reëntering the solution. Such a state of affairs renders the use of the Gibbs' adsorption equation a very doubtful aid in interpreting surface tension data from protein solutions. So far, surface tension studies on protein solutions have not been related except in a very vague fashion to the other physical properties of proteins.

Methods

The surface tension of protein solutions is extremely difficult to measure accurately and, in spite of the very large literature on the subject, it may be fairly stated that the equilibrium surface tension of such solutions has never been determined. It is characteristic of the surface tension of protein solutions to drop progressively with time, and the unstable character of the molecule, together with the marked tendency to become infected with foreign organisms, precludes the possibility of extended measurements, so that equilibrium observations cannot be made. Quite apart, however, from this serious handicap, there are other factors which limit very seriously the techniques which can be used.

As pointed out in the previous section, an insoluble film is formed at a protein solution surface. It is probable that this film is highly organized, with the protein molecules oriented (10). If the film is disturbed during the course of the surface tension measurement, the film organization is disrupted and the tension measured bears little relation to that in its quiescent condition. This fact alone renders the du Noüy tensiometer more or less valueless for such measurement. Johlin (82) has pointed out how extremely critical the ring and wire diameters are for this method. The use of the ring method (du Noüy) for the measurement of the surface tension of protein solutions is to be discouraged.

The formation of threads of coagulated protein induces inaccuracies in the capillary rise method. The reviewers have observed that even in the absence of protein threads the column of protein solution is apt to stick at points removed from equilibrium in much the same manner that a column of dirty mercury fails to show the true pressure in a mercury manometer. It is evident that, since the surface tension of protein solution changes so drastically with time, such methods as the drop weight and maximum bubble pressure method of Sugden give only a measure of the dynamic tension, which has little significance for the structure of protein films.

The sessil bubble method as employed by Johlin (85) seems to be free from these objections. Unfortunately, this method is relatively insensitive, and Johlin reports also that the values one obtains are, for unknown reasons, apparently too high. The reviewers feel that the method of Wilhelmy (141), as developed by Harkins (69), holds very attractive possibilities for the measurement of the surface tension of protein solutions. Bull (22) has applied this method to determine the surface tension of egg albumin solutions with very gratifying results.

Table 1 shows the attempts which have been made to measure the surface tension of protein solutions. In spite of the relative character of most of these measurements they are, with one or two exceptions, in broad qualitative agreement. We shall now discuss these results with respect to protein concentration, time, pH, and salt concentration.

Protein concentration

In general, as the protein concentration is increased the surface tension decreases, sharply at low concentrations and reaching more or less of a limiting value at higher concentrations. Various workers (29, 37, 71) have reported maxima and minima in the surface tension as protein con-

TABLE 1

Surface tension studies on proteins

PROTEIN	METHOD	VARIABLES	WORKERS
Egg albumin and hemoglobin	Sugden bubble pressure	pH, heat denaturation	Loughlin (103)
Gelatin	Sessil bubble	Time, pH, protein concentration	Johlin (85)
Serum proteins	Capillary rise	CO_2 content	Johlin (83)
Gelatin	Drop weight and capillary rise	pH, time	Johlin (80)
Casein, egg albumin, hemoglobin	Capillary rise	Time, protein concentration	Johlin (81)
Gelatin	Sugden bubble pressure	pH	St. Johnston and Peard (87)
Caseinogen, egg albumin	Sugden bubble pressure	Electrolytes, pH	St. Johnston (86)
Egg albumin, serum albumin, gelatin	Stalagmometer	pH, anions	Errera and Millan (38)
Gelatin	Drop weight	pH, protein concentration	Davis, Salisbury, and Harvey (28)
Gelatin	Stalagmometer	pH, electrolytes	Artom (5)
Gelatin	Capillary rise	pH	Jermolenko (79)
Serum albumin, gelatin, egg albumin	Ring (du Noüy)	Time, pH, protein concentration	de Caro and Laporta (30)
Casein, egg albumin, serum albumin	Stalagmometer	pH, heat denaturation	Berczeller (12)
Egg albumin, serum proteins	Ring (du Noüy)	Time, protein concentration	du Noüy (37)
Egg albumin	Drop weight	pH, time, concentration	Fu and Wu (42)
Various proteins	Capillary rise and stalagmometer	pH	Bottazzi*
Egg albumin	Wilhelmy balance	pH, protein concentration	Bull (22)

* Atti Accad. Lincei **21**, II, 221, 561; **22**, II, 141.

centration is progressively increased. It is the reviewers' opinion that such irregularities are in most cases artifacts. Certainly the Wilhelmy and sessil bubble methods disclose no such complicated relations. It appears that such irregularities could arise from (*1*) changes in the hydrogen-ion concentration in unbuffered solutions, (*2*) surface contamination by surface-active materials, and (*3*) inherent defects in the techniques employed. It is possible to realize a broad minimum in the surface tension of colloidal substances, such as sodium oleate (83), and presumably such a situation could arise in protein solutions, but the reviewers feel that such a relation has not as yet been established for protein systems. Incidentally, the minimum in the sodium oleate–surface tension curve is attributed to association of particles at higher concentrations and has nothing to do with a change of orientation at the surface. The above remarks apply specifically to the efforts of du Noüy and other workers to evaluate molecular dimensions from surface tension data.

If no molecules were able to leave the surface after having entered, the surface should in time saturate itself at the concentration where there was just a sufficient number of molecules in solution to occupy completely the available surface. Further increase in concentration should produce no further change in surface tension. As far as can be judged from the extrapolation of the surface tension to infinite time (see page 399), this is not the case, since even at relatively high egg albumin concentration (0.2 per cent) the surface tension is still slightly dependent on concentration. Two possible explanations for this dependence suggest themselves: (*1*) when the solution surface is covered or nearly covered with denatured protein film, it is impossible for a molecule entering the film from the solution to surface denature, since it has to expand or unfold to do so, and, accordingly, it remains in the soluble native state, in which condition it can pass again into the solution and thus establish an equilibrium for this part of the film, or (*2*) the soluble native molecules are adsorbed on the bottom surface of the denatured film and affect the surface tension indirectly through their influence on the denatured molecules in the film. It may turn out, however, that if and when true equilibrium surface tension measurements are made on solutions of such proteins as egg albumin, the surface tension of the more concentrated solutions will be found to be independent of concentration.

Johlin (85) found that when equilibrium surface tension values of gelatin solutions are plotted against the logarithm of the concentration, a gentle curve was obtained, which departs from a straight line in both the dilute and the concentrated solutions (equilibrium values were obtained with the sessil bubble method after a 24-hr. wait).

Time

All workers agree that the surface tension of protein solutions changes greatly with time, and that this change takes place over a number of hours. du Noüy (37) reports that surface tension follows the relation

$$\sigma = \sigma_0 e^{-Kt^{\frac{1}{2}}}$$

where σ is the surface tension after time t, σ_0 is the initial surface tension, and K is a constant. Johlin (81) criticized this expression and suggested that the surface tension of protein solutions may, except for a very short interval at the beginning, be expressed as a function of time in the form

$$\sigma = \frac{a}{t^n}$$

where a and n are constants. When log σ was plotted against log t, a straight line was obtained which allowed the evaluation of the constants. Bull, using the Wilhelmy method and solutions of egg albumin in $N/150$ sodium acetate buffer, found that plot of log σ against log t did indeed yield straight lines, but only after about 100 min. If the reciprocal of time be plotted against surface tension, a curve is obtained with a very gentle slope at longer times; such a curve can be extrapolated to zero reciprocal time with reasonable safety, and yields an estimate of the surface tension at infinite time. This technique probably gives the closest approximation for an equilibrium value for the surface tension of protein solutions that is obtainable. By this method of estimation Bull (22) found that above a concentration of 0.02 per cent of egg albumin in $N/150$ sodium acetate buffer at pH 4.90, the surface tension was only slightly dependent on protein concentration (a drop of about 1 dyne per centimeter between 0.02 per cent and 0.20 per cent). The surface tension at 0.02 per cent protein was about 47 dynes per centimeter, which corresponds to a film pressure of 25 dynes per centimeter. Interestingly enough, this is the film pressure at which an inflection in the straight line is observed in the pressure–area curve for a film of spread egg albumin on $N/150$ sodium acetate buffer at pH 4.90. Evidently a film on a protein solution can spontaneously attain the film pressure of a highly compressed spread film.

Some workers (30) report a minimum in the time–surface tension curve. Such a minimum could be occasioned by an association of the protein molecules in the surface, i.e., a reaction between molecules. While it is not possible to say definitely, the existence of such minima in the surface tension–time relation of protein solutions seems improbable. It is more probable that such minima as have been reported are due to film plasticity incident with the gelling of the film and have nothing to do with true surface tension. Such minima are not found with the capillary rise or the Wilhelmy method, but are frequently observed with the ring (du Noüy) method.

The reason for the prolonged change of surface tension of protein solutions with time is obscure, although two possibilities suggest themselves. It is conceivable that the polypeptide chains are highly organized (10) in the completed film, and it might require considerable time for these unfolded, extended chains to orient themselves in the very viscous surface film into positions which yield the minimum free energy. The second possibility, which may be involved as well as the one given above, is that the surface film is being penetrated by native molecules from the solution, which denature in so far as space is available for them to do so (see page 398). It is certain, at least in the case of egg albumin in appreciable concentrations, that the surface is practically saturated within a few seconds after formation, and native molecules arriving from the interior of the solution would find only a small fraction of the surface available for penetration. Accordingly, only a small fraction of the molecules which strike the surface would be effective in lowering the surface tension. This would be expected to prolong the attainment of equilibrium.

The slow attainment of the final value for the surface tension is definitely not due to a slow rate of diffusion of the protein to the surface, as can be seen from the following approximate calculations.

If all the molecules diffusing to the surface remain at the surface, i.e., if the rate of diffusion is the limiting factor in the attainment of equilibrium, the number of molecules in 1 sq. cm. of the surface after time t is given by the following relation (93)

$$n = 2n_0\left(\frac{Dt}{\pi}\right)^{1/2}$$

where n_0 is the number of molecules per cubic centimeter and D is the diffusion coefficient (this equation assumes an infinite depth of solution). From spread film studies on egg albumin, we know the number of molecules per square centimeter corresponding to a given film pressure. If we assume, as a first approximation, that the film formed on a protein solution is analogous in this respect to a spread film, we may calculate the number of molecules per square centimeter of solution surface at any time, t, by comparing the surface tension with the film pressure of spread films. Table 2 shows the number of egg albumin molecules arriving at a surface of a 0.05 per cent solution as calculated from the diffusion equation given above. These values are compared with the number per square centimeter of solution surface estimated from the surface tension of 0.05 per cent egg albumin in $N/150$ sodium acetate buffer at pH 4.90, and the film pressure of a spread film of egg albumin on a $N/150$ sodium acetate buffer at pH 4.90. From these approximate calculations it can be seen that a sufficient number of protein molecules had diffused to the surface in 0.58 sec. to saturate the surface completely; hence it may be concluded that diffusion is not a limiting factor.

Hydrogen-ion concentration

Proteins being ampholytes, it is to be expected that hydrogen ions would have pronounced influence on the surface tension of protein solutions. This, in general, is found to be the case, although the various workers are by no means in quantitative or even qualitative agreement concerning this influence.

TABLE 2

Number of molecules of egg albumin diffusing and on the surface

t IN SECONDS	$n \times 10^{-12}$ DIFFUSING	$n \times 10^{-12}$ ON SURFACE
0.10	2.32	
0.58	2.50	
1.00	7.37	
5.00	16.5	
30.00	40.4	
60.00	57.0	1.85
300.00	127.0	1.96
600.00	180.0	2.04
1800.00	312.0	2.17
3600.00	441.0	2.32
7200.00	625.0	2.38
		2.50

Almost every publication dealing with the surface tension of protein solutions has a section on the influence of hydrogen ions. It hardly seems worth while to review this literature in detail. After considering the matter, the reviewers have decided to limit the discussion to the careful work of Johlin (85), who employed the sessil bubble method to measure the surface tension of gelatin and to the work of Bull (22), who used the Wilhelmy balance method to measure the surface tension of egg albumin solution.

Johlin (85) followed the surface tension of gelatin solutions for 24 hr. at pH values from 0.0 to 12.0. He found the surface tension to drop progressively, although he states that at the end of 24 hr. the system had reached equilibrium, as evidenced by no further fall in surface tension. The pH–surface tension curves at the end of 1 and 3 hr. had the same general contour, although at the end of 3 hr. the surface tension over the whole pH range was about 5 dynes per centimeter lower than at the end of 1 hr. These curves exhibited a sharp maximum at pH 2.0 with a broad minimum at pH 4.6 (isoelectric zone), a fairly sharp rise to pH 8.0, and a flattening off of the curve beyond this pH. The 24-hr. curve (equilibrium) had an entirely different contour from those of the 1- and 3-hr. curves. There was no maximum in the acid region, the surface tension–pH curve rising from about 45 dynes per centimeter at pH 0 to about 50 dynes per centimeter at pH 3.5, with a flatter portion between this pH and pH 5.0 (isoelectric zone), with a sharp rise at pH 6, and with a broad maximum at pH 9.0. Johlin states that the pronounced fall in surface tension in the acid region may have been due to acid hydrolysis of the gelatin, although it is difficult for the reviewers to see why acid hydrolysis would be expected to lower the surface tension, as amino acids have no pronounced capillary activity. It is possible that the acid may have brought about some structural changes in the gelatin molecules, and it might prove worthwhile to investigate other physical properties of gelatin which had been exposed to an acid medium for 24 hr.

Bull (22), using the Wilhelmy balance method and solutions of egg albumin, followed the surface tension from 1 min. to 3 hr., and, by extrapolating the surface tension–reciprocal of time curve to zero reciprocal of time, estimated the surface tension at infinite time. He studied the region between pH 2.8 and pH 9.5. There was no pronounced change in the contour of the surface tension–pH curves with the passage of time, although the surface tension of the more alkaline solutions tended to drop somewhat faster than in the isoelectric or acid ranges. A sharp maximum in surface tension was found at pH 3.2 with a broad minimum at pH 5.0 (isoelectric point of surface-denatured protein) and with an increase starting at pH 5.5 and continuing to a maximum at pH 8.0, but for the longer time this maximum was lost and the curve flattened off at pH 6.0. The surface tension in the alkaline regions was considerably less than in the acid region. The fact that a minimum was observed in the isoelectric zone indicates that the electrocapillary effects are not important, since from these considerations a maximum surface tension would have been expected at the isoelectric point.

Electrolytes

The reviewers have been unable to find any clear-cut results dealing with the effect of electrolytes on the surface tension of protein solutions, and data are badly needed on this point. One would expect, in general, that the presence of electrolytes would tend to reduce the influence of hydrogen ions and to bring the surface tension of both acid and basic solutions to that at the isoelectric point.

ADSORPTION OF PROTEINS AT A SOLID–SOLUTION INTERFACE

Landsteiner and Uhliz (89) were among the first to study protein adsorption at a solid–solution interface. They worked with the proteins of horse serum and were able to show that various inorganic powders adsorbed or removed a high percentage of the protein from solution.

Michaelis and Rona (108) investigated the adsorption of "peptone" by kaolin and charcoal. They stated that the amount of "peptone" adsorbed is independent of the volume of solution employed. They also noted the irreversibility of "peptone" adsorption and concluded from their experiments that the adsorption of "peptone" is not entirely a physical process but involves a chemical reaction.

Biltz (14) studied the adsorption of "albumin" by cellulose, ferric oxide, and kaolin. He found that the amount adsorbed varied with protein concentration and that the adsorption was nearly irreversible.

During all of these early years there were numerous papers dealing with the stabilizing and sensitizing of colloidal suspensions with proteins. The reviewers cannot deal with this phase of protein adsorption.

Loeb (102) studied the rate of flow of water through collodion membranes that had been allowed to come in contact with proteins. He found evidence for adsorption of proteins by the membranes. Hitchcock (73) extended the measurements of Loeb and measured as well the actual amount of egg albumin and gelatin adsorbed per gram of collodion membrane. The adsorption reaction for both proteins followed Langmuir's adsorption equation rather than that of Freundlich. This might be taken as some evidence of only one layer of molecules in the adsorbed film. Hitchcock also found that the maximum adsorption for both proteins came close to their respective isoelectric points, although the maximum adsorption of egg albumin was somewhat on the basic side of the isoelectric point and was at pH 5.0. This last point may be of some significance, since it is now known that the isoelectric point of surface-denatured egg albumin is at pH 5.02 (112).

Palmer (122) further investigated the adsorption of gelatin on collodion disks and found that, although the amount of protein adsorbed was strongly dependent on the pH at low protein concentrations, above 10 per cent protein the amount adsorbed was independent of the pH. He further was able to show that the presence of salts in protein solutions of less than 10 per cent tended to nullify the effect of pH and to increase the amount of adsorption. He considered that his findings confirmed Loeb's theory of the association of gelatin particles.

Dow (35) extended the protein adsorption studies on collodion disks by measuring the adsorption of egg albumin from 0.10 to 23.00 per cent protein concentration as a function of pH and of salt concentration. He found that at higher protein concentrations (about 8 per cent) the adsorption curve experienced a discontinuity toward increased adsorption. He observed again a maximum adsorption at pH 5.0 in the absence of salts, while in the presence of sodium chloride the amount adsorbed on the acid side of pH 5.0 became equal to that adsorbed at pH 5.0, and on the basic side of pH 5.0 the amount adsorbed was considerably greater than that at pH 5.0 (about 400 per cent greater). Dow was unable to explain the effect of salts on egg albumin adsorption. Loeb's theory of association of protein particles had been evoked to explain the action of electrolytes on the adsorption of gelatin, and the similar behavior of egg albumin in the presence of electrolytes was somewhat embarrassing, since egg albumin molecules are considered not to be associated. The reviewers are inclined to feel that the action of electrolytes on the adsorption is essentially electrostatic in nature and that electrolytes decrease the electrostatic repulsion between protein molecules, thus allowing them to approach closer on the collodion surface; accordingly, a greater adsorption is experienced per unit area. The electrolytes would also decrease the force of repulsion on the basic side of the isoelectric point between the mutually negatively charged protein and collodion and allow the more capillary-active, negatively charged protein molecules (see page 403) to be adsorbed to the greatest extent.

Dow made the rather extraordinary observation that the adsorption of egg albumin at 25°C. was approximately twice that at 1°C.; it is well known that adsorption reactions in general have a temperature coefficient less than 1.

Incidentally, there is some question in the minds of the reviewers in regard to Dow's work, since, in order to have well-mixed systems, the containers were rocked at the rate of 60 oscillations per minute for 18 hr. Under these conditions it is quite possible that an appreciable quantity of the egg albumin had been surface-denatured, and this would obscure the significance of the experiments.

Langmuir and Schaefer (94) have used an optical method for the determination of the thickness of what they designate as S-layers of protein. These films are produced by placing a drop of protein solution on a wet plate upon which have been deposited A-layers of stearic acid conditioned with aluminum chloride solution. The protein is washed off and the plate dried. Then from the change in color of light given by interference from the top and bottom of the film, the thickness is calculated. They found that such a film formed from a 1 per cent egg albumin solution was 50 Å. in thickness. Tobacco virus protein gave a thickness of 300 Å. on a stearic acid surface conditioned as described above, while on a surface conditioned with egg albumin, the thickness of the S-layer of tobacco virus was 125 Å.

In a later publication Langmuir and Schaefer (95) report that better adsorption is obtained if a barium stearate surface is conditioned with thorium nitrate instead of aluminum chloride. With a 1 per cent egg albumin solution the thickness of the S-layer with thorium nitrate was 48 Å., with aluminum chloride 33 Å., and with thorium silicate 35 Å. They make no comment on the revision of their previous value for the thickness on an aluminum chloride conditioned surface from 50 Å. to 33 Å.

Langmuir and Schaefer (96) have extended their study of S-layers to urease and pepsin. They conditioned barium stearate monolayers with thorium dioxide and stated that if the conditioned barium stearate surface was dried before the drop of urease solution was placed on it, an A-layer of urease was formed instead of an S-layer. The S-layer of urease was 35 Å. thick and had great urease activity. They also formed S-layers of urease by placing a drop of urease solution on a wet, clean glass slide. The slide was washed and dried and heated for 16 hr. at 100°C. The urease film on such a slide retained a strong urease activity.

S-layers of pepsin on conditioned barium stearate were 13 Å. thick (Lilly pepsin) and 29 Å. thick (Northrop pepsin) and retained their milk-clotting properties.

The reviewers find it difficult to evaluate the above experiments. The variable thicknesses encountered with the same, as well as with different, conditioning agents speak for a very ill defined layer of adsorbed protein. The thickness is, in general, not sufficient for a monolayer of native protein, and it is too thick for a monolayer of surface-denatured protein. It is possible that the S-layer is a mixture of native and denatured protein.

Of considerable interest for the subject of protein adsorption is the work of Lindau and Rhodius (100). These investigators used gelatin to determine the adsorbing surface of quartz powder. They accomplished this by adsorbing gelatin on quartz plates of known dimensions, and then, knowing the area which corresponded to a given weight of adsorbed gelatin, they were able to calculate, from the amount of gelatin adsorbed by the powder, the area of adsorbing surface per unit weight of powder. It was necessary in this calculation to assume that the adsorption of gelatin per unit area was the same on the quartz plates as on the quartz powder. Having determined the area of the quartz powder in the above fashion, they were then ready to study the adsorption of egg albumin on the quartz powder.

They found that the adsorption of egg albumin followed Langmuir's adsorption isotherm. They extrapolated the adsorption curve to saturation and were thus able to estimate the amount of egg albumin adsorbed at saturation of the quartz surface. They checked this amount by placing the powder in a concentrated solution (about 1 per cent) of the protein, washing the powder with distilled water, and determining the amount of egg albumin remaining on the powder. The two methods gave very satisfactory checks. They concluded from these experiments that the protein was irreversibly adsorbed on the quartz. They did not establish, however, that the irreversibly adsorbed protein was the only protein adsorbed, i.e., there may have been a reversibly adsorbed layer on top of the irreversibly adsorbed layer. Using 34,500 as the molecular weight of egg albumin and assuming the closest packing of spheres, they arrived at 43 Å. as the thickness of irreversibly adsorbed protein. This value, they pointed out, agrees well with that reported by Svedberg from ultracentrifugal studies. If one recalculates their data, using the specific volume of egg albumin and assuming complete coverage, a thickness of 24.6 Å. is found for the adsorbed protein layer.

The reviewers consider it rather remarkable that protein adsorption which is apparently irreversible can be described in terms of the Langmuir adsorption equation. As is known, this equation was derived by postulating an equilibrium between particles leaving and entering the surface, and if the particles are irreversibly adsorbed, it is hard to see how such an equilibrium could be established. It may be that it is only when the surface is completely or nearly completely covered with protein that the adsorption becomes irreversible, and that this irreversibility is due to the attraction of the protein molecules for each other as well as for the quartz. In other words, the protein becomes coagulated on the surface. At any point less than saturation, the protein molecules would be separated on the surface and would not coagulate, and, accordingly, could leave as well as enter the surface. The fact, however, that Langmuir's adsorption equation is followed, as is shown not only by the work of Lindau and Rhodius but also by that of Hitchcock *et al.*, constitutes another objection to du Noüy's technique for the estimation of the thickness of the adsorbed layer of protein, since it was necessary for du Noüy to assume that all of the protein had been adsorbed out of solution onto the surface.

Lindau and Rhodius (100) also investigated the hydrophilic properties of quartz powder upon which known quantities of egg albumin had been adsorbed. They found that, up to 50 per cent saturation of the surface, the surface had practically the same hydrophilic properties as that of the uncovered quartz, while at 58 per cent coverage the surface became abruptly very hydrophobic and continued to become progressively more so as the amount of egg albumin on the powder was increased. This finding is extremely interesting; it goes hand in hand with the irreversible character of egg albumin adsorption, since molecules which formed a hydrophobic surface would have little tendency to leave the surface and reënter the solution. It also suggests that it is only when the adsorbing surface is covered to the extent of 58 per cent or more with protein that the protein is irreversibly adsorbed. The hydrophobic character of the film at higher per cent coverage indicates that in adsorption the polar side chains of the protein are directed toward the quartz with the hydrophobic side chains toward the water. It seems probable that such a drastic distortion of the molecule would lead to denaturation.

Lindau and Rhodius (100) determined the amount of egg albumin adsorbed on quartz powder at pH 3.19 and pH 11. They found that the amount of protein adsorbed at these pH values was much less (23 and 7.3 per cent, respectively, of the isoelectric value) than the amount adsorbed at the isoelectric point; on this basis they assumed that the egg albumin molecule swells away from its isoelectric point and occupies a much larger volume and, accordingly, that it takes less protein to saturate the surface. It is to be regretted that Lindau and Rhodius prepared their egg albumin from a commercial stock of dried powder, so that the purity of their preparation is open to suspicion.

There have been a number of investigations of protein adsorption of a somewhat less detailed nature than those given above. Ettisch, Domontowitsch, and Mutzenbecher (39) studied the adsorption of egg albumin, hemoglobin, and serum albumin on collodion membranes. Paic and Deutsch (120) investigated the effect of hydrogen ions on the adsorption of hemoglobin on kaolin and later (121) the influence of electrolytes on the adsorption of hemoglobin on kaolin. Deutsch (31) extended the work on the adsorption of hemoglobin and later (32) investigated the adsorption of serum albumin on kaolin. Spiegel-Adolf (139) reported on the adsorption of serum albumin, pseudoglobulin, and euglobulin by aluminum hydroxide suspensions and by mastic sols.

ELECTROKINETIC STUDIES ON PROTEIN SURFACES

Electrokinetic technique offers a very elegant method for the study of certain aspects of surface reactions of proteins. The reviewers recommend very strongly the careful work and methods of Abramson (1) and Moyer (111) to those interested in making use of this technique for protein study.

The reviewers cannot attempt to describe the methods or theory of electrokinetics or deal with the electrokinetics of proteins in general, but must confine themselves to a review of that work which throws some light on the surface reaction of proteins.

Brossa and Freundlich (18) apparently were the first to coat suspended particles (ferric oxide sol) with protein (beef serum albumin), to study the electrophoretic mobility of such coated particles, and to realize the nature of the measurements they were making. Loeb (101) later used this method to study the electrokinetic behavior of gelatin; in this work collodion particles were coated with gelatin. Freundlich and Abramson (43) investigated in some detail the electrokinetic behavior of inert particles placed in various concentrations of gelatin, albumin, and hemoglobin. They were able to show that the mobility of the inert particles was lowered by the presence of 10^{-7} g. of protein per liter of solution, that at 10^{-4} g. of gelatin per liter saturation had been reached, and that the addition of further protein was without effect. In both the Loeb and the Freundlich–Abramson measurements the inert particles were large enough to be visible under the microscope, and the electrophoretic mobility was determined by means of the microscopic method. Since this early work a number of investigators (17, 128) have employed this method. Abramson and Moyer have been especially active in exploring the exact relation between the electrokinetic behavior of dissolved protein and the same protein coated on inert particles of microscopic size.

Apparently in some cases the dissolved protein has the same electrokinetic properties as the adsorbed (serum albumin (113), pseudoglobulin (114)), while other proteins show a difference (egg albumin (112), carboxyhemoglobin (36), and oxyhemoglobin (36)). The question of whether or not the protein shows identical electrokinetic properties in the dissolved as well as in the adsorbed state is important, because it gives us some clue as to whether or not the protein is denatured upon adsorption. Thus, egg albumin in the dissolved state is isoelectric at pH 4.52 (112), and the surface-coagulated protein is isoelectric at pH 5.02 (112), while inert particles coated with egg albumin are isoelectric at pH 4.82 (112); this indicates that adsorbed egg albumin may be partially denatured. It may be that the intermediate value is due to the adsorption of some native as well as denatured protein. It would be interesting in this relation to wash the adsorbed surface thoroughly and redetermine the isoelectric point. It might be found that the isoelectric point had risen to that of the surface-coagulated protein.

The work of Dummett and Bowder (36) is hard to interpret, owing to their unfortunate mistake of using the hydrodynamic equations for a flat electrophoretic cell instead of those for a cylindrical cell, with which they worked. The isoelectric points, however, should be reliable, and these indicated that both carboxyhemoglobin and oxyhemoglobin had undergone considerable change upon adsorption (except at a copper surface). Dummett and Bowder reported that adsorption on the inert particles proceeds very quickly and that in 0.01 per cent gelatin equilibrium is reached in a few seconds, while with 0.0012 per cent gelatin equilibrium is reached in about 3 min. They also reported that the nature of the underlying surface is very important in influencing the electrokinetic behavior of proteins, but, owing to their failure to use the proper hydrodynamic equations, their results in this respect cannot be properly evaluated. Moyer (112) found that the electrophoretic mobility–pH curve for egg albumin is rotated somewhat around the isoelectric point for different surfaces (aluminum oxide, quartz, and silica gel), but that the isoelectric point is independent of the nature of the surface.

It is very curious that the microscopic, inert particle covered with protein behaves electrokinetically as if it had the radius of a protein molecule and not its own radius (114). The reason for this fortunate but surprising behavior is unknown.

Martin (105) studied the rate of adsorption from 0.0002 per cent gliadin solutions on a fritted-glass diaphragm by means of streaming potential measurements. Equilibrium as judged by the streaming potential was reached in from 10 to 50 min. after the glass had come in contact with the protein solution. His data indicate no clear relation between the time for the streaming potential to reach equilibrium and the sign or magnitude of the electrokinetic potential.

Kemp and Rideal (88), using the Mattson cylindrical cell, studied the electrophoretic mobility of quartz powder suspended in gliadin solutions in respect to time, protein concentration, salt concentration, and pH. They found that for a given pH the mobility follows the equation:

$$\Delta u \quad \frac{KC}{1 + K'C}$$

where K and K' are constants, C is the gliadin concentration in grams per cubic centimeter, and Δu is the difference in mobility between that of the uncoated quartz and of the quartz in equilibrium with a given protein concentration; mobility is expressed in centimeters per second per volt per centimeter. The relation is analogous to a Langmuir adsorption equation and indicates a possible proportionality between mobility and the amount of protein adsorbed. Making such an assumption Kemp and Rideal found that the adsorption of gliadin on quartz was reversible, and that the rate of adsorption followed a unimolecular reaction rate. The adsorption of the positively charged gliadin (pH 3.7) on negatively charged quartz was considerably faster than that of negatively charged gliadin (pH 5.66) on negatively charged quartz. This indicates that, while the electrokinetic potential is important in protein adsorption, it is not the only factor to be considered.

II. Spread Protein Monolayers

Devaux (33) was, apparently, the first to spread protein ("albumin") on pure water and to study the properties of such spread films. He found a film thickness of from 30 to 80 Å.

Metcalf (107), in a brilliant paper in 1905, described the study of "peptone" films spread on water. He devised several types of surface viscometers which he employed to measure the viscosities of spread films of peptone.

During the last decade considerable information has accumulated regarding the properties of spread monolayers of proteins. The fact that before spreading many proteins are soluble in the medium upon which they are to be spread, while the spread film of protein is insoluble, suggests that, in general, proteins undergo drastic structural changes during spreading. Investigations of spread films of proteins have furnished valuable data for the interpretation of protein structure. A notable fact arising from this film work is that intrinsic differences between native proteins largely disappear upon spreading. Thus, the thickness of protein film is approximately the same for all proteins, whereas proteins in the native, dissolved state differ greatly in their molecular dimensions.

The properties of spread protein monolayers and the methods used for their investigation will be discussed in the following sections.

Technique of spreading

Proteins are dissolved in a suitable solvent (usually water) and the protein solution transferred to the surface on which spreading is to occur. As most proteins are water-soluble, there is considerable danger of a portion of the protein being lost in the underlying liquid, and accordingly very exact and careful technique has to be followed in placing the protein solution on the surface.

Gorter and Grendel (51, 54) blow about 0.005 cc. of a protein solution out of a micropipet held horizontally along the surface. Neurath (115) found that Gorter and Grendel's method may be safely modified by allowing larger volumes of a more dilute protein solution to be dropped on the surface from a height of a few millimeters. The method used by Bull (20), at the suggestion of Dr. D. R. Briggs of the University of Minnesota, consists in dipping a calibrated 1-cc. pipet vertically into the surface. After withdrawing it slightly, so that a cone of liquid is formed around the tip of the pipet, the protein solution is forced out gradually by means of a screw arrangement. Apparently, as the film spreads out from the spot where the protein has been applied it drags water along with it and produces a convection upward and along the surface. This convection tends to bring into the surface any material which had passed into the bulk solution.

Hughes and Rideal (77), Hughes (76), and Fosbinder and Lessig (40) found that solid particles, even of water-insoluble protein, spread very rapidly when carefully placed on the surface. The amount of spread material is determined by means of a modified Nernst balance. As dissolution occurs very much faster at the edge of the solid particle exposed to the surface than from parts of the particle immersed in the water, the risk that protein is lost in the interior of the solution is very small (3, 25).

Philippi (125) has called attention to the discrepancy between the film areas of gliadin as spread by Gorter and Grendel's method, on one hand, and those spread by the method of Hughes and Rideal, on the other. Recent investigation of this problem by Mitchell (109) shows that the area of protein films spread from solution varies with the protein concentration of the spreading solution and attains maximum values only with very dilute solutions. If sufficient time for complete spreading is allowed, monolayers of gliadin spread from a 0.01 per cent solution are almost identical with those obtained by spreading from solid protein.

Homogeneity of protein films

To be able to interpret data obtained from a study of spread monolayers, it is necessary to be certain of the homogeneity of the spread films. The results found by various experimenters working with the same protein sometimes differ widely from one another, and the suspicion arises that the lack of agreement is due to incomplete or imperfect spreading. If the film area is too large, it may be due to contamination of the surface by other surface-active materials or by dust, while too small areas result from incomplete spreading or collapse of the film under unduly high pressures.

Hughes and Rideal (77), Philippi (124), and others have employed surface potential measurements to test film homogeneity. In the case of homogeneous films the surface potential does not vary more than 2 to 3 millivolts as the electrode is moved over the monolayer. Fluctuations in the surface potential from place to place on the film have been found to occur at very low pressures (77), or if the pH and electrolyte concentration of the underlying solutions were not well chosen (59, 124). Also, compression of the film prior to complete spreading may lead to large fluctuations of the surface potential.

Zocher and Stiebel (146) developed a very ingenious method of testing film homogeneity. They observed the film, which was illuminated by light coming through a dark field condenser of the cardioid type located in an opening in the bottom of the trough, with a microscope. It is easy to detect film inhomogeneities with this method, since light is not scattered by a homogeneous monolayer under these conditions, while any unspread material or aggregates formed incidental to collapsing of the film show up as brilliantly illuminated regions. By moving the film under the microscope by means of two rigidly connected barriers, a large portion of the film can be examined. A simplification of Zocher and Stiebel's method has been introduced by Adam (2). Hughes and Rideal (77) found films of gliadin, glutenin, and egg albumin to exhibit brilliant collapsed patterns. If the collapsing occurred during compression, long folds perpendicular to the direction of compression were in evidence. Similar patterns have been observed by Neurath (115) with serum albumin at pH 4.8 and at film pressures greater than 14 dynes. Zocher and Stiebel reported that solid films of serum globulin were very inhomogeneous, as indicated by optical examination. Casein was found to form homogeneous films when spread on $N/10$ hydrochloric acid, whereas numerous small colloidal particles, imbedded in the solid film structure, could be detected if this protein were spread on distilled water.

Influence of time on the spreading of proteins

The time necessary for complete protein spreading is, in general, longer than that required by other film-forming substances. Gorter and Philippi (59) and Philippi (124) have followed the rate of spreading of egg albumin by means of surface potential measurements. Owing to the fact that the surface potential of a clean water surface differs greatly from the surface potential of the film-covered surface, the film boundary can be readily detected. The time of spreading was found to vary greatly with the pH and electrolyte concentration of the underlying solution. A minimum value of 2 min. was observed at the isoelectric point, while on the acid side the spreading time increased with decreasing pH, and attained a maximum value of 2 hr. at pH 3.80. The spreading time decreased again at pH values below this point, and at pH 1.07 spreading was complete after 10 min. On the alkaline side the spreading time increased with increasing pH, and 9 hr. were required for complete spreading at pH 5.72. If the pH was higher than 6.0, no homogeneous film could be obtained. Philippi's observations strongly suggest that the variation of film areas with pH reported by many authors for a large number of proteins (see following sections) is due to incompletely spread films resulting from insufficient time being allowed for spreading, and that likewise the lack of spreading at the isoelectric point of some proteins (137) may be due to similar causes.[1]

The influence of pH on spreading time can be greatly diminished by the addition of electrolytes. At pH 3.9, for instance, the addition of $N/80$ potassium chloride decreases the spreading time of egg albumin from 2 hr. to 5 min., and at pH 5.7 from 9 hr. to 2 hr. (125). Anions are more effective in reducing the spreading time of positively charged protein than are cations, and polyvalent anions are more effective than univalent anions. Cations have a greater influence on the alkaline side of the isoelectric point than do anions. Philippi's results indicate that it is the net charge on the protein molecule that determines the rate of spreading; the greater the net charge, the smaller the rate of spreading. The presence of a net charge on the protein molecule tends, apparently, to prevent the molecule from passing from the bulk of the underlying solution into the surface and is, no doubt, due to mutual repulsion of the electrostatic charges of like sign.

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[1] Bence-Jones protein, for instance, continues to spread even 5 hr. after placing the material on an isoelectric buffer solution. Also, urease spreads very slowly under similar conditions (56).

Surface pressure measurement of protein films

Before discussing the properties of protein monolayers, it may be well to survey briefly the methods employed for their investigation. Most of the experimenters have used a surface balance of the type described by Langmuir (90), Adam (3), and Harkins (70). A simplified type of Adam's balance has been described by Gorter (62); it lacks, however, the accuracy of Adam's instrument in the lower pressure region. The Central Scientific Company manufactures a surface balance under the trade name of the Cenco hydrophil balance, which yields satisfactory results if not too high accuracy is required.

A very simple method for measuring the surface pressure of films of fatty acids, proteins, etc., has been reported by Blodgett (15). Certain types of oil, such as oxidized lubricating oil, have the property of spreading into thin films which exhibit interference colors. The higher the degree of oxidation of the oil, the thinner the film will be. Such oils are called indicator oils. Very thin films are colorless, while brilliant interference colors appear as the film thickness is increased. Calibration of the interference colors against film pressures, by means of a surface balance, gives a convenient method of measuring film pressures up to 10 dynes. When protein is placed in the center of an indicator oil film, the protein spreads out, displacing the oil and leaving a clear, colorless area occupied by the protein. Upon lateral compression of the combined oil–protein film, successive interference colors appear on the oil film and indicate the exerted film pressure (90). One point about the indicator oil technique troubles the reviewers; is there complete protein spreading under the film pressure exerted by the oil film? Protein films produced under these circumstances may not be entirely homogeneous.

Gorter and Seeder (60) have suggested a method for measuring film areas at zero compression. By means of an electrically operated tuning fork, waves are produced on the surface, and their dampening due to the presence of the film is observed. The interpretation of the results is, however, so difficult that this method has hardly been used for protein work.

PROPERTIES OF SPREAD PROTEIN FILMS

Spreading power

Comparison of the spreading tendency of various proteins reveals that not all proteins spread with equal ease at their respective isoelectric points (125). Egg albumin (20, 59, 65, 124, 125, 136), serum albumin (53, 115), insulin (63), pepsin (47, 125), zein (63), and others spread readily and completely, whereas proteins such as the respiratory protein of *Palinurus vulgaris* (125), fibrinogen (57), myosin (64), and tobacco virus (137) spread very poorly, if at all, when placed on the surface of an isoelectric buffer solution. Heat-coagulated egg albumin and serum albumin also spread very poorly, if at all (115). If the underlying buffer solution be adjusted to a pH outside of the stability range of the respective protein, a non-spreading protein can usually be induced to spread (50, 125). Philippi (125) has classified proteins into two classes in respect to spreading power: (*1*) those which spread on a buffer at the isoelectric point and (*2*) those which do not spread at the isoelectric point, but do spread outside of their stability region. The reviewers feel that the failure of some proteins to spread is due to the intramolecular cohesive forces being too strong to permit unfolding of the polypeptide chains on the surface.

The addition of a small amount of a proteolytic enzyme induces spreading of the non-spreading proteins. Thus, trypsin enhances the spreading of fibrinogen (57), myosin (64), and denatured egg albumin (49). If the enzymatic action proceeds too far, spreading becomes incomplete (49, 64), owing, no doubt, to the great solubility of the split products resulting from protein hydrolysis.

A lack of spreading has also been observed with gelatin and protamins (50). These proteins have a very high solubility in water, and it appears that dissolution in the underlying solution occurs before unfolding on the surface can take place.

Pressure–area relations of isoelectric protein films

By plotting the pressure exerted on a monolayer against the area of the film, a curve is obtained which can be interpreted in terms of the structure of the monolayer (3). Such curves are so similar for the various proteins that identical film structures for all proteins have been postulated (40, 44, 53, 77). Generally, the compression curves for protein films may be roughly divided into two regions. The first extends from zero compression to about 3 dynes, and the second, which is the high compression region, from 3 dynes up to the collapse pressure. Proteins such as serum albumin, lactoglobulin (125), and gliadin (77) exhibit, however, another region at very low pressures (0 to 0.3 dyne), where the surface pressure is independent of film area. Such proteins expand indefinitely at zero pressures. Egg albumin and pepsin, on the other hand, do not spread over the entire surface at zero pressure but form rigid coherent films (125). Whether or not such protein membranes form, depends, in the reviewers' minds, merely on the strength of the cohesive forces acting between the polar side chains of the protein film and on the degree of "fitting" of these side chains, rather than on any fundamental difference of structure between these two groups of protein films. The so-called surface patterns of proteins, described by Langmuir (92), seem to be due to similar causes.

At pressures between 0.2 and 1 to 2 dynes the slope of the pressure–area curve increases rapidly. Films which are in the liquid state when completely expanded may become solid when the film pressure attains these values. Measurements of the surface potential, to be described in a following section, reveal that the change of slope of the force–area curve in this low pressure region is due, not merely to packing of the protein molecules, but also to a change in the orientation of the side chains of the amino acid residues. This change of orientation is, apparently, complete when the force–area curve becomes linear with increasing pressure. This linear portion, which is really only approximately linear and is the second region mentioned above, begins at about 3 dynes and extends to about 20 dynes. In this high-pressure region hysteresis (41, 77, 125) of the film has been observed. It is not associated with changes in the surface potential, and equilibrium pressures are usually attained after a few minutes (41).

It has been the custom to extrapolate this linear portion of the force–area curve to zero pressure and characterize the protein film by the area found by such an extrapolation. The reviewers feel that such an extrapolation has no theoretical justification, and a far more significant area would be the area found by extrapolating the pressure–area curve in the lower pressure region to zero pressure or, better still, to consider the area of the film where the coefficient of compressibility is at a minimum. Since, however, most workers have published their results in terms of the extrapolation of the linear part of the pressure–area curve to zero pressure, we shall, for convenience, summarize their findings on this basis. This is done in table 3 for proteins spread on buffers at the isoelectric points of the proteins.

Table 4 shows the corresponding data for proteins which can be spread only outside of their stability zones or by the addition of proteolytic enzymes.

TABLE 3

Limiting areas of isoelectric protein films, obtained by extrapolation of the linear part of the force–area curve to zero pressure

PROTEIN	COMPOSITION OF MEDIUM	pH	AREA PER MILLIGRAM IN SQUARE METERS	OBSERVER
Egg albumin	$N/300$ acetate buffer	4.8	0.88	Gorter, van Ormondt, and Dom (65)
Egg albumin	$N/20$ acetate buffer	4.8	0.88	Neurath (115)
Egg albumin	$N/300$ acetate buffer	4.8	0.93	Ter Horst (140)
Egg albumin	$N/300$ acetate buffer	4.5	1.06	Philippi (125)
Egg albumin	$N/150$ acetate buffer	4.9	1.04	Bull (20)
Egg albumin, heat-denatured	$N/150$ acetate buffer	4.9	0.99	Bull (20)
Egg albumin, urea-denatured	$N/150$ acetate buffer	4.9	0.98	Bull (20)
Egg albumin, urea-denatured	Citrate–phosphate buffer	7.0	1.84	Lee and Wu (99)
Egg albumin	$N/300$ acetate buffer	4.6	1.10	Fourt and Schmitt (41)
Serum albumin	$N/20$ acetate buffer	4.8	1.04	Neurath (115)
Serum albumin	$N/10$ KCl + HCl	4.36	1.08	Philippi (125)
Pepsin	$N/100$ KCl + HCl	2.80	0.92	Philippi (125)
Pepsin	HCl	2.90	1.00	Gorter (47)
Pepsin	HCl	2.70	1.10	Seastone (137)
Trypsin		7.0	1.00	Gorter (47)
Lactoglobulin	$N/200$ acetate buffer	5.3	0.98	Philippi (125)
Insulin	$N/300$ acetate buffer	5.4	1.07	Philippi (125)
Insulin	$N/300$ acetate buffer	5.0	0.88	Gorter and van Ormondt (63)
Oxyhemoglobin	Phosphate buffer	6.8	0.60	Gorter and Grendel (44)
Gliadin	Phosphate buffer	5.9	1.1	Hughes and Rideal (77)
Zein		5.3	1.1	Gorter and van Ormondt (63)
Cytochrome C	K_2CO_3	10.0	1.2	Harkins and Anderson (68)
Insulin*	$N/100$ H_2SO_4		1.75	Mitchell (109)
Insulin*	$N/100$ H_2SO_4		1.23	Mitchell (109)
Gliadin*	$N/100$ H_2SO_4		1.18	Mitchell (109)
Zein*	$N/100$ H_2SO_4		1.50	Mitchell (109)

* Spread on the acid side of the isoelectric point.

Although the film areas given in tables 3 and 4 seem to be nearly the same for all proteins, closer inspection of the pressure–area curves reveals some deviation from such a uniform behavior. As the slope of the pressure–area curve is indicative of the compressibility of the film, it is of interest to compare the compressibilities of a number of proteins with one another. The coefficient of compressibility is defined as

$$-\frac{1}{A_0}\left(\frac{\mathrm{d}A}{\mathrm{d}F}\right)$$

where A_0 is the film area found by extrapolating the linear portion of the pressure–area curve to zero pressure and $\mathrm{d}A/\mathrm{d}F$ is the reciprocal of the slope of the linear portion of the pressure–area curve (20). Compressibilities expressed in this manner vary from 16×10^{-3} cm. per dyne for egg albumin to almost twice this value for gliadin. The compressibility of protein films probably reflects in some manner the interaction between side chains of the amino acid residues in the protein molecule. The reviewers feel that it would be very profitable to calculate the compressibilities over the entire pressure range. With this mode of calculation A_0 would be the area of the film at the point at which the slope of the line is determined. Making such calculations for egg albumin spread on $N/150$ acetate buffer at pH 4.9, a distinct minimum in the coefficient of compressibility is found at 14 dynes. This point undoubtedly corresponds to fundamental changes in the film. Incidentally, the minimum compressibility is reached considerably before the pressure–area curve begins to depart noticeably from its linear course.

TABLE 4

Limiting areas of protein films. Spreading induced by acids or by enzymes

PROTEIN	SPREADING INDUCED BY	pH	AREA PER MILLIGRAM IN SQUARE METERS	OBSERVER
Myosin	Trypsin	7.3	1.0	Gorter and van Ormondt (64)
Fibrinogen	Trypsin	4.7	0.7	Gorter, Maaskant, and Van Lookeren Campagne (57)
Casein	Hydrochloric acid ($N/10$)		1.0	Gorter and Grendel (52)
Bence-Jones	Hydrochloric acid	1.0	0.8	Gorter and Maaskant (56)
Urease	Hydrochloric acid	1.0	1.0	Gorter and Maaskant (56)
Hemocyanin Limulus	Hydrochloric acid	1.0	1.4	Seastone (137)
Vaccinia	Hydrochloric acid	1.0	0.7	Seastone (137)
Heat-denatured egg albumin	Pepsin		About 1.0	Gorter (49)
Nerve protein	Alcohol	4.6	0.80	Fourt and Schmitt (41)

Collapsing of isoelectric protein films

Monolayers of proteins collapse at lower pressures than those of most substances. Indications of collapsing may be furnished by optical examination, surface potential measurements, or by a flattening out of the pressure–area curve at high pressures (68). As the critical pressure which produces collapsing may greatly depend on the rapidity of compression, pH (68, 115), temperature (140), and the presence of impurities (140), the collapsing pressures recorded in the literature are not very significant. The film areas which correspond to the collapse point are presumably the smallest area which the protein molecule can occupy in a homogeneous monolayer, and, accordingly, collapse points are of considerable significance when determined unambiguously (3, 68). It may turn out that the point of minimum compressibility defines with exactness the collapsing pressure. The collapse pressure of a protein film is greatest at its isoelectric point. Thus, films of egg albumin collapse below pressures of 15 dynes at pH 4.4, and films of serum albumin at 11 to 12 dynes when spread under similar conditions (115). Gliadin collapses at 15.8 dynes, zein at 10.5 dynes, and insulin at 10 dynes when spread on $N/100$ sulfuric acid (109).

TABLE 5

Compressibilities of protein films spread on isoelectric buffer solutions

PROTEIN	COEFFICIENT OF COMPRESSIBILITY IN CENTIMETERS PER DYNE	CALCULATED FROM DATA OF
Egg albumin	0.0160	Philippi (125), Bull (20)
Egg albumin	0.0145	Neurath (115)
Serum albumin	0.0242	Philippi (125)
Serum albumin	0.0230	Neurath (115)
Lactoglobulin	0.0187	Philippi (125)
Gliadin	About 0.028	Hughes and Rideal (77, 3)
Cytochrome C	0.029	Harkins and Anderson (68)
Palmitic acid	0.0021	Adam (3)

Bull (20) has extended surface pressure measurements of egg albumin to pressures as high as 40 dynes. At about 25 dynes the pressure–area curve swings up again. The hydrophilic properties of the film, as measured by the adhesion tension for water of the film deposited on glass slides under various pressures, remain more or less constant from 25 to 31 dynes. Above 31 dynes the film becomes suddenly more hydrophobic. Upon reëxpansion of these highly compressed films and extrapolation to zero pressure, about 30 per cent of the material was found to have been lost, either by dissolution or by aggregation into polymolecular aggregates.

Influence of temperature

Ter Horst (140) has carried out interesting investigations of the influence of temperature on the properties of compressed, and of uncompressed but coherent, films. Observations made 2 hr. after spreading show that increase of temperature produces an increase of film area, irrespective of pH. The temperature had its least influence at pH 2.8 and its greatest at the isoelectric point and at pH 1. It is interesting to note that the influence of temperature is greater on fully spread compressed films than on the uncompressed but coherent film. From the readings it would appear that at about 50°C. the areas of the compressed film (obtained by extrapolation of the linear part of the compression curve to zero pressure) and of the coherent film will be identical. Increase of temperature apparently decreases the angle of tilt of the side chains to the surface, and at sufficiently high temperatures they are lying flat on the surface both in the compressed and in the uncompressed states.

Influence of pH and electrolyte concentration of the underlying solution

Gorter and his associates introduced the term "spreading number" to designate the film area in square meters per milligram of protein. The area is found by extrapolation of the linear part of the pressure–area curve to zero pressure. By measuring the pressure–area relations at a standard short time after placing the material on the surface, a spreading number is obtained which is suitable for comparative purposes. The spreading number was found by these workers to vary with the pH of the trough solution. As a rule, if the spreading number is plotted against pH, a W-shaped curve is obtained. A maximum value is observed at the isoelectric point with minima on both the acid and the alkaline side of the isoelectric point.

Such curves, or at least indications of them, have been observed with egg albumin (61, 65), pepsin (47), trypsin (47), casein (52), zein (63), oxyhemoglobin (44), insulin (63), cytochrome C (68), and others. Also, the tripeptide of α-aminocaprylic acid shows a similar dependency upon pH. The extent of variation of the spreading number with pH varies from protein to protein, and is probably intimately connected with the number and strength of the ionic groups of the protein molecule. Gorter and his associates also found that, at pH regions in which little spreading occurs, maximum spreading may be obtained merely by the addition of salts. It was found that the salts followed the order of the lyotropic series (46) in their ability to increase spreading. The influence of pH can also be greatly diminished, and even completely suppressed, by combining the protein with certain organic acids or bases, prior to spreading.

Thus, the addition of tartrazine (66) restores completely the spreading of egg albumin on the acid side of its isoelectric point, and the addition of spermidine (66) aids the spreading of pepsin on the alkaline side of the isoelectric point of this protein. Protamine is effective in suppressing the pH influence on insulin (45). From the point of view of spreading power, such combined proteins behave no longer as zwitter ions but as polyvalent cations or anions, respectively (49). Mere addition of a proper amount of the organic compounds to the trough solution produces similar effects (66). The increased expansion of monolayers of myosin when spread on potassium lactate solutions has been reported by Moss and Rideal (110).

Gorter and Philippi's observations on the influence of time on the spreading of proteins (see page 412) threw new light on this problem. If sufficient time, prior to compression, is allowed for spreading to become complete, the spreading of a given protein is independent of the pH and the ionic strength of the underlying solution. It is only if compression of a film is started before complete spreading that the spreading number is small. It is true, however, that under certain conditions the spreading process is so slow that complete spreading cannot be obtained.

There exists, however, a considerable influence of the pH and the ionic strength of the underlying solution on the area of completely spread, uncompressed, or slightly compressed protein films. It has been mentioned previously that certain proteins, such as egg albumin and pepsin (125), form coherent, monomolecular membranes of considerable rigidity, even at very low pressures. The area of these coherent films has been found to be constant over a pH range of 4 to 5.5 for egg albumin. At pH values lower than 3.9 the area increases with decreasing pH, the films becoming less homogeneous and less rigid (124). On the alkaline side of this "stability zone" the film area decreases with increasing pH. Proteins which do not form rigid coherent films at low pressures show a similar pH dependency if they are compressed to an area which is greater than that found by extrapolation of the linear part of the compression curve to zero pressure. In these cases, however, the area increases on either side of the isoelectric point. Serum albumin exhibits a "stability zone" between pH 4.9 and pH 8, whereas in the case of insulin the pH range of constant film area is very narrow, around pH 5.5. The pH dependency can also be observed by keeping the film area constant and recording the film pressures in relation to pH (125).

The increase of film areas with pH may be related to the ionization of the polar groups of the film molecules. It will be remembered that ionization of the end groups of long chain acids or amines increases tremendously the expansion of monolayers of these substances. The formation of gaseous films, under these conditions, has been correlated with the repulsive forces acting between the ionized groups of the molecules (3). Although in the case of protein films the end groups are not free to move about on the surface independently, there is ample evidence to believe that they lie flat on the surface at low pressures. The variations of film areas with pH may, therefore, be ascribed to repulsive forces acting between ionized end groups of these side chains. It is only if the net charge of these zwitter-ionic groups is sufficiently high that the effects of the pH on the film areas become noticeable.

Surface potential measurements

Measurements of the change of the potential difference between a liquid and air, produced by the presence of a monolayer, have been used frequently for investigations of surface films. The arrangement generally used consists of a movable, radioactive electrode above the surface, a reversible electrode in the trough solution, and a potentiometer–electrometer circuit which permits measurements of the surface potential difference between the air–liquid interface (3). Detailed descriptions of the apparatus have been given by Schulman and Rideal (134), Adam and Harding (4), Harkins (67), Philippi (125), and others. The surface potential difference between a clean surface and a film-covered surface may be expressed by the equation:

$$\Delta V = 4\pi\mu n \tag{1}$$

where ΔV is the potential difference in millivolts, n the number of molecules per unit surface, and μ the vertical component of the dipole moment of the film molecules. This equation is an approximation, as it neglects the forces between film molecules and water molecules, the interaction between neighboring film molecules, and the rearrangement of dipoles and ions of the underlying solution (3). In spite of these limitations, determinations of μ from surface potential measurements have furnished suggestive data concerning the rearrangement of film molecules during compression. If no rearrangement takes place, μ should be constant within a certain compression range. Variations may be ascribed to a change of the angle of tilt of the film molecules to the surface, according to the following equation:

$$\mu = \frac{\bar{\mu} \cos \theta}{D} \tag{2}$$

where μ is the observed dipole moment, $\bar{\mu}$ the actual dipole moment, θ the angle of tilt, and D the dielectric constant of the medium. The influence of rearrangement of water molecules and ions and of the polarization of oriented molecules by neighboring molecules is hardly evaluable and presents a serious difficulty in the interpretation of surface potential data.

Rideal and his associates (76, 77, 135) and Gorter and his school (59, 124, 125) have applied surface potential measurements to protein monolayers. On the basis of equation 1, the surface potential plotted against film areas should give a straight line as long as no rearrangement of film molecules occurs. Adam (3) has recalculated Hughes and Rideal's (77) data on gliadin spread on $N/100$ hydrochloric acid and found μ to be constant at areas beyond 1.3 sq. m. per milligram. Likewise Philippi (125) found values of $\Delta V \times A$ to be constant if the area of monolayers of serum albumin or lactoglobulin was greater than 1.0 sq. m. per milligram of protein. Similar results have also been reported for egg albumin (124). At pressures above about 1 to 2 dynes per centimeter the slope of the potential-area curves decreases with increasing pressure. This change of the slope has been ascribed to a change of orientation of film molecules, as well as to dehydration occurring during compression. Philippi (125) believes that the change of μ upon compression is mainly due to dehydration of the film. In an earlier publication Philippi (124) supported the view of Hughes and Rideal (77), which has been shared by Adam (3), Ter Horst (140), Mitchell (109), and others, that the change of the dipole moment is mainly due to side chains being forced out of the plane of the surface during compression. This view is also shared by the reviewers and will be discussed in a following section (see page 426).

The surface potential of protein films varies markedly with the pH of the underlying solution. ΔA-area curves are usually shifted upwards and are parallel to each other as the pH is decreased.[2] Similar changes have been observed with fatty acids, the surface potential being higher in the unionized than in the ionized state (132). Even negative potentials may arise from ionization of the end groups. Adam (3) has ascribed this to the fact that in the unionized state the molecules are oriented with the positive carbon of the carboxyl group above the negative oxygen, whereas dissociation produces the formation of an additional dipole of opposite direction, the positive hydrogen ion below, and the negative oxygen above. The resultant moment of these oppositely directed dipoles will determine the total difference in surface potential. As similar changes with amines are of much smaller magnitude, the total effects observed with zwitterionic proteins may well be explained on that basis.

Philippi (125) has attempted to evaluate the maximum charge on a protein monolayer from surface potential data, using a modification of Chapman's (26) and Herzfeld's (72) equation for the drop of the interfacial tension of a water surface when it becomes electrically charged. The calculated values are considerably lower than those derived from acid- and base-binding capacity. The disagreement has been ascribed to a decrease of the dipole moment due to penetration of counter ions between the polar heads of the film molecules. The variations of film pressures with pH, mentioned in the previous section, have been related by Philippi to the electric repulsion between charged film molecules and counter ions, respectively, and to osmotic forces exerted by the counter ions. Neglecting any specific adsorption, he has calculated, with the aid of Chapman's and Herzfeld's equations, the film pressure variations from the corresponding surface potential data. It is the reviewers' opinion that such considerations, although of considerable interest, are somewhat premature at the present stage of our knowledge.

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[2] If the ionic strength of the medium is sufficiently high, the surface potential is independent of pH.

The influence of denaturation on protein spreading

Undoubtedly native proteins denature upon spreading. The extensive structural changes involved, as is shown by the radically altered molecular dimensions, permit of no other conclusion. There is, unfortunately, considerable misunderstanding concerning the term "denaturation." We employ it here to mean a profound structural change in the protein molecule, and it involves, as recent work indicates, a change from a condensed to a more extended molecular configuration (9, 21, 118). Such denatured protein is readily soluble away from its isoelectric point. Coagulation, on the other hand, is a change of the soluble protein (denatured or native) to an insoluble condition. There is reason to believe that compressed protein films are coagulated as well as denatured. Devaux (34) was able to show that such films have no solubility at all. On the other hand, at very low film pressures the amount of protein adsorbed from very dilute solutions into the surface film was a function of the amount of protein in solution (34), indicating that in expanded films the protein is denatured but not coagulated. This point deserves the attention of investigators.

Lee and Wu (99) showed that urea-denatured egg albumin can be completely spread on a buffer at pH 7.0. Bull (20) was able to spread both heat-denatured egg albumin and urea-denatured egg albumin on a buffer at pH 4.9, providing the protein solutions being spread were first adjusted to a pH of 2.2. Further, he was able to show that both these forms of denatured egg albumin, as well as native protein, when spread, gave practically the same pressure–area relations, indicating an identical structure for these three spread substances.

If the solution of denatured protein from which spreading is to take place is too close to the isoelectric point, spreading will not occur, as Neurath has shown (115). Evidently the denatured protein is coagulated on the surface before it can spread. Gorter (49) has shown that the addition of traces of pepsin restores completely the spreading power of heat-denatured (coagulated) egg albumin in much the same manner as trypsin aids the spreading of proteins which otherwise can be spread only on dilute acids. Heat-coagulated egg albumin, without the use of enzymes, will definitely not spread.

Rideal (130), Neurath (115), and Gorter (45) have investigated the action of ultraviolet light on the properties of completely spread protein films. It was found that the films collapse under the influence of irradiation; the film area becomes smaller with increasing time of irradiation. Ultraviolet light of different wave lengths seems to produce different effects (130).

Langmuir (92) has recently reported that the so-called "surface patterns," produced by placing an "indicator oil" on top of a protein film, are different for spread denatured proteins than for spread native proteins. The reviewers are unaware of the experimental details of these investigations and cannot, therefore, evaluate the significance of these findings.

Structure of protein monolayers

Numerous attempts have been made to relate the observed properties of protein films to the structure and orientation of the film molecules. As it is impossible in this review to give due consideration to all the various hypotheses which have been advanced, the readers are referred to the original papers. The following discussion merely outlines the reviewers' opinion regarding this problem.

There is considerable evidence for the assumption that, in the completely expanded form, protein monolayers consist of polypeptide chains of the beta-keratin type (11), with the amino acid residues stretched out flat along the surface (53, 76, 77, 109, 124). If 3.5 Å. be taken as the length of a peptide group in the direction of the chain and 4.5 Å. as the average length of a side chain (11), and if allowance is made for alternate orientation of the side chains, the calculated minimum area is 31.5 sq. Å. This value is to be compared with the values listed in table 6, column 5. The mean areas per amino acid residue in sq. Å., *Ar*, given in table 6 were calculated according to the following relation:

$$Ar = \frac{A \times Mr \times 10^{23}}{6.06 \times 10^{23}}$$

where *Mr* is the average molecular weight per residue and *A* the film area in square meters per milligram of protein.

The agreement between areas calculated in this manner and those calculated from molecular dimensions is, considering the assumptions involved, in satisfactory accord. The approximate values for the average residue weight, the average length of the side chains, and the limiting area at zero compression may well and readily account for the slight deviations.

Hughes and Rideal (77) and Mitchell (109) reported higher values than those given in table 4 for the areas of gliadin, zein, and insulin per amino acid residue. These films, however, were spread on $N/100$ hydrochloric acid, which is well on the acid side of the isoelectric point of these proteins, and under these conditions electrostatic repulsive forces between ionized end groups would tend to keep the side chains apart. This is indicated by the fact that when gliadin is spread on a phosphate buffer at pH 5.9, the limiting area per residue is 32.8 Å.

TABLE 6

Observed and calculated film areas of proteins

PROTEIN	AVERAGE RESIDUE WEIGHT	LOW-PRESSURE REGION EXTRAPOLATED TO ZERO PRESSURE			HIGH-PRESSURE REGION AT COLLAPSING PRESSURE			
		Area per milligram	Film thickness	Mean area per residue	Area per milligram	Film thickness	Mean area per residue	
							All R groups on one side	Alternate orientation of R groups
		square meters	Å.	*square meters*	*square meters*	Å.	*square* Å.	*square* Å.
Egg albumin (20, 115, 125)	124 (12)	1.3	5.7	27.5	0.77	9.6	15.9	31.8
Insulin (109, 125)	122 (78)	1.65	4.5	33.0	0.77	9.6	15.5	31.0
Serum albumin (115)	134 (27)	1.45	5.1	32.0	0.79	9.4	17.2	34.2
Gliadin (3, 77)	120 (109)	1.65	4.5	32.8	0.50	About 15	10.0	20.0
Cytochrome C (68)	120*	1.55	4.9	30.6	0.70	10.0	14.0	28.0

* Estimated.

Evidence is also available from the study of the tripeptide α-aminocaprylic acid (58). When this tripeptide is spread at pH 4.6, the limiting area is about 93 sq. Å., and since the calculated area per molecule with the side chains lying flat on the surface is 116 sq. Å., but only about 50 sq. Å. if they are perpendicular to the surface, it may be assumed that the side chains are lying flat.

We have noted in our preceding discussion that certain proteins form rigid, coherent films in the low-pressure region, whereas others are in the liquid state (50, 92, 125). There is, no doubt, a tendency for the polar group of neighboring peptide chains to attract each other and, similarly, the non-polar groups have a "mutual solubility." Such a state of affairs would tend to give a certain structure or rigidity to the film. Whether or not a coherent film is obtained depends, in the reviewers' opinion, mainly on the degree of "fitting" of the end groups; close fitting would bring the side groups within the sphere of their attraction and tend to produce a coherent film. The influence of pH on the properties of expanded protein films, mentioned in a previous section, may likewise be accounted for on the basis of the above picture. Repulsive forces, evoked by conferring positive or negative charges on the protein film, will greatly decrease the lateral adhesive forces between neighboring polypeptide chains.

The thickness of a fully extended protein film, using the density of protein in bulk, is about 5 Å.

Lateral compression of expanded films produces drastic changes in the orientation of film molecules, as is indicated by a gradual decrease in the dipole moment and by a decrease in the coefficient of compressibility. Also, the films which are liquid in the low-pressure regions become rigid on compression. In addition (20), it has been observed that the adhesion tension between films deposited on glass and water drops sharply at 1.5 dynes pressure.

While slight compression may merely cause the protein molecules to close in laterally without change in orientation of the side chains (77, 109), undoubtedly under higher pressures the side chains will be forced out of the surface until they are oriented perpendicular to the surface. The reorientation is probably complete when the slope of the pressure–area curve attains its maximum value. Closest packing will, however, be attained only at very high pressures near the collapse point.

It is possible to obtain some information regarding the structure of highly compressed films from the areas occupied by such films and from the molecular dimensions. If the protein molecules have a fully stretched beta-keratin configuration, then the area per residue should be 15.7 sq. Å. (11). This value agrees with the area per residue as calculated from film areas if it is assumed that all side chains are on the same side of the plane (table 6, column 8). As, however, the side chains are essentially of hydrocarbon nature, their minimum film area cannot be less than between 20.5 and 25 sq. Å. (3). Alternate orientation of the side chains would yield ample room for them in the film. It is to be expected that polar side chains would be directed towards the water and the apolar chains towards the air. Since in a number of proteins about one half of the total residues are polar and the other half apolar (105, 125), the minimum area per amino acid would be about 31.5 sq. Å. This value is compared with the calculated film areas in table 6, column 9. If there is a large excess of apolar or polar side chains, the area per residue at the collapse point would be somewhat larger than calculated on the assumption of alternate orientation (109).

The thickness of protein films at the collapse point is likewise in good agreement with this picture. Column 7 of table 6 lists the respective values. They are in the neighborhood of 10 Å., which is the value assigned to the side chain spacing of the beta-keratin from x-ray studies. The film thickness should be only about 5 Å. if all side chains were oriented on the same side of the surface. The investigation of the structure of deposited monolayers of egg albumin by means of x-rays confirms the idea that the side chains are oriented perpendicular to the surface (10).

The rigidity of the compressed films may, in addition to the action of residual affinities between peptide linkages of neighboring chains, be ascribed to the adhesion between now vertically close-packed side chains.

Compression of the films in the high-pressure region probably results also in a dehydration in the film (40, 77, 109, 125). In fact, Philippi (125) attributes the decrease in area of the film on increasing pressure, even in the low-pressure regions, to a dehydration of loosely bound water. It should be pointed out, however, that Philippi tacitly assumed that all residues are directed towards one side of the surface in low pressures and towards both sides in the high-pressure region, but did not explain the change of orientation during compression. The reviewers have indicated their reasons for believing that the change in orientation of side chains from a horizontal to a vertical position is mainly responsible for the pressure–area relations in the low-pressure region and that such dehydration as does occur is incidental.

Stereochemical considerations and valence angle requirements seem to rule out any folding of the polypeptide chains upon compression. As all naturally occurring amino acids are structurally related to *l*-lactic acid, the orientation of the residues will be alternate in a *fully* extended polypeptide chain; partial or complete ring formation, however, would result in all residues attached to carbon atoms of a ring being oriented on the same side of the plane. It may be readily seen that neither the alpha-keratin, nor the "supercontracted"-keratin configuration (7), nor any other ring structure would allow sufficient room for the vertically oriented side chains in the film and would result in areas per residue much smaller than those observed.

Wrinch (143) advanced the theory that protein films consist of "cyclol" fragments, i.e., cages broken down into plane fragments, held together either by hydrogen bonds or else by salt linkages. It is a requirement of such a structure that the side chains be on the front surface of the network, out of the water, whereas peptide hydroxyl groups emerge from both surfaces of the network. The area per amino acid residue has been given as about 10 sq. Å. for polymers of "cyclol 6", and as 13.3 and 16.8 sq. Å., respectively, for less dense structures, such as polymers of "cyclol 18" and "cyclol 66". The actual available areas are, in the reviewers' opinion, probably even smaller, owing to the uneven distribution of side chains within the network, and owing to the spaces taken up by peptide hydroxyls. As, according to Wrinch's view, protein films retain at least fragments of cyclols, it follows that in the densest spots of the film there cannot be enough room for the side chains, which require a minimum surface area of between 20 and 25 sq. Å. Similar considerations may be applied to the surface requirements of closed cyclols, such as the C_2 molecule, which has been assigned to the structure of proteins of the 40,000 molecular weight class.[3] The assumption that ionized side groups which emerge from the upper surface are bent so that they lie in the water phase would add to the difficulty of fitting this hypothesis to the area requirements, since a bent chain should occupy a greater cross-sectional area than if it were straight.

Rideal (131), Philippi (125), and Mitchell (109) have pointed out that a protein monolayer may be regarded as a triplex film which consists of an upper hydrocarbon layer of low dielectric constant and of a thickness of about 3.5 to 4.5 Å. Below this layer is the middle layer, formed by the main chains and associated water molecules, and finally below the middle layer are the polar side chains.

Very little is known about the structural changes which proteins undergo during spreading. Gorter (50) and Neurath (115) have described the process as an unfolding of polypeptide chains. Astbury (7) has suggested that spreading brings about a separation of disks which, in the native molecule, are about 10 Å. apart. It is the reviewers' belief that a final elucidation of this problem, which is so intimately connected with the problems of protein structure and denaturation, must await further work in the field of protein chemistry.

Mixed films

By means of surface potential and surface pressure measurements, Rideal, Schulman, and Hughes investigated associations and interactions between proteins and other surface-active materials (104, 131, 133, 135, 136). Digestion of egg albumin and caseinogen films by pepsin and trypsin, dissolved in the underlying solutions, has been studied by Schulman and Rideal (135). From the studies, as far as they have gone, these authors concluded that the disappearance of a protein film on an enzyme-containing substrate is due only to digestion and not to adsorption of some capillary-active constituents of the enzyme. This viewpoint has been revised as a consequence of further detailed investigations (133) concerning the behavior of protein monolayers on solutions containing surface-active substances.

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[3] A detailed discussion of this problem is in preparation and will be published elsewhere.

Injection of a surface-active substance underneath a surface film has been found to affect greatly the surface potential and surface pressure of the film. Mere anchoring of the injected molecules by suitable polar groups of the film alters the surface potential without changing the surface pressure. Thus, gallic acid, tannic acid, or certain dyes are adsorbed beneath protein monolayers without penetrating them. If, however, there is in addition to polar interaction a strong attraction between the hydrophobic groups of the material beneath the film and the hydrophobic groups of the film molecules, the injected molecules penetrate the film. Such penetration can readily be detected by a considerable increase of surface pressure, which is well above the possible film pressure of either of the components individually. Film pressures of as high as 60 dynes have been observed with stable mixed films (136). Complete film penetration will cause the surface potential to become identical with that of a mixed film containing equimolecular proportions of the two molecules at maximum compression (133). Stable mixed films have been obtained with gliadin and cholesterol up to film pressures of 20 dynes (136). Film penetration may increase or decrease the rigidity of a protein monolayer, depending on the pH and the electrolyte concentration. Triolein completely liquefies a gliadin film, but gelation takes place upon strong compression of a mixed gliadin–tripalmitin film (136). If the interaction between the molecules of two components of a mixed film is weak, lateral compression will force one molecular species out of the film. Thus, a stable and rigid cholesterol–gliadin film liquefies suddenly at pressures above 20 dynes, revealing all the characteristics of a cholesterol film (136). It is of interest that this process is reversible. Likewise, monolayers of egg albumin have been reported to become displaced by injection at pH 7.2 of long-chain fatty acids underneath the film. Film penetration may be completely prevented by compressing the film, prior to injection, to the equivalent pressure at which displacement would start. The significance of the phenomena of film adsorption, penetration, and displacement, respectively, for agglutination, sensitization, and hemolysis has been pointed out by Schulman and Rideal (136).

The properties of mixed films of egg albumin and myristic acid, obtained by simultaneous spreading of these substances from solution, have been investigated by Neurath (117). By assuming that the protein occupies the same film area in the presence of the acid as it does when spread alone, no film interaction could be detected with films containing between 100 and 400 molecules of myristic acid per molecule of protein. With films containing less myristic acid, a marked increase of the area per fatty acid molecule was observed, and with a mole ratio of 9 reached a value of more than 180 sq. Å.

Protein films deposited on solids

Langmuir and his associates, following the technique which had been used with stearate monolayers, have carried out interesting experiments[4] in which spread protein films were deposited on solid surfaces (16). Langmuir, Schaefer, and Wrinch (97) have described the properties of monolayers of egg albumin transferred to chromium plates on which layers of barium stearate had been deposited. The results obtained have been taken as support for the view that protein monolayers consist of a two-dimensional network and not of polypeptide chains. Neurath (116) has pointed out that, under the conditions of these experiments, the occurrence of film collapsing prior to deposition has to be envisaged and that the properties of such films may be accounted for in terms of inhomogeneous, collapsed layers. The lack of a well-defined hydrophobic or hydrophilic character of deposited protein monolayers has been explained by Langmuir (91) on the assumption that protein monolayers may "overturn" in response to the conditions under which they have been deposited. The reviewers find it difficult to reconcile this hypothesis with the view that protein films consist of a two-dimensional network. Whereas polypeptide chains could be expected to possess the degree of flexibility which, according to Langmuir's picture, is necessary for overturning of stearate films, considerable constraint must be imposed upon the flexibility of protein films if they consist of a two-dimensional network.

Langmuir and Schaefer (96) reported that monolayers of urease and of pepsin, deposited on conditioned plates, have a high chemical activity as measured by the decomposition of urea and by the clotting of milk, respectively. The data indicate that monolayers of urease were active only when deposited as B-layer, whereas in the case of pepsin both A- and B-layers were active. The reviewers believe that, in view of the general importance of such studies, severely controlled experimental conditions are of utmost necessity. Langmuir and Schaefer report that monolayers of urease were obtained by spreading on distilled water at pH 5.8. Gorter and Maaskant's (56) experiments seem to indicate, however, that in that pH range the spreading of urease requires more than 16 min. to be complete. It may also be pointed out that, according to Langmuir and Schaefer's data, active monolayers of urease vary in thickness from 11 to 21 Å. when deposited under 0.4 dyne pressure, whereas the thickness of a homogeneous protein film is about 5 Å. at low pressures and hardly exceeds 10 Å. even near the collapsing pressure. Likewise the thickness of 14 Å., reported for active monolayers of pepsin, seems to be too high for a homogeneous monolayer.

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[4] In view of the forthcoming publication of a summarizing article by Dr. Langmuir in this Journal, the reviewers have refrained from a detailed discussion of his work on protein monolayers.

Gorter (48) reported that monolayers of pepsin and trypsin, removed from the surface by a silk gauze and dissolved again in buffer solution by proper adjustment of the pH, retained about 80 per cent of their original activity. These results have been taken as proof that either the monolayers themselves are active or else that the activity has been regained upon dissolution of the surface-denatured enzyme.

Astbury, Bell, Gorter, and van Ormondt (10) have deposited up to seventeen hundred successive layers of egg albumin on chromium-plated metal slides. These films have a tendency to tear parallel to the direction in which the slide was moved through the liquid phase. They are birefringent when viewed perpendicular to the surface, the slow vibration being parallel to the direction of movement of the slide. Some of the films investigated showed numerous boat-shaped holes (negative tactoids) pointing parallel to the direction of movement of the slide. The thickness of these films, measured by direct mechanical means, has been found to be 9.5 Å. per monolayer, in excellent agreement with the results obtained with the surface balance.

The influence of deposited layers of fatty acids and proteins on the changes in shape of mammalian erythrocytes has been investigated by Ponder and Neurath (127). From the results obtained these authors concluded that a red cell can hemolyze when less than half of its surface is in contact with a monolayer of a lytic substance, and even when there are not enough lysin molecules to cover the whole cell surface with a monolayer.

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